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[DRAFT FOR CONSULTATION]

Drugs for Chronic Hepatitis C Infection — Cost-Effectiveness Analysis

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Methods

An economic model was developed in the form of a cost-utility analysis of drugs for chronic hepatitis C infection. The primary outcome was the number of quality-adjusted life-years (QALYs), with treatments compared in terms of the incremental cost per QALY (incremental cost-utility ratio [ICUR]). Treatments included in the base-case analysis were treatments that have price information and have met the inclusion criteria of the protocol. Newer treatments (i.e., daclatasvir and asuneprevir) met the inclusion criteria but price information was not publicly available, therefore these agents were included in exploratory analyses. Treatment effect estimates on sustained virologic response (SVR) and relative risk of adverse events (anemia, depression, and rash) were obtained from the network meta-analyses (NMAs). Other inputs for the economic model were derived from published sources and validated by clinical experts. Drug costs were obtained from the Ontario Drug Benefit Exceptional Access Program, Yukon Drug Formulary, the Saskatchewan Drug Benefit, or directly from manufacturers. Extensive sensitivity analyses were conducted to test the effect of changes in underlying parameter values (parameter uncertainty) and assumptions within the models (structural uncertainty).

Summary of Findings

Key Economic Findings

The results of the base-case analysis suggest that for each genotype 1 population (treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic or treatment-experienced cirrhotic), at least one of the interferon-free therapies appears to be economically attractive compared with pegylated interferon alfa combined with ribavirin (PR) alone. The drug that is the most cost-effective varies by population, but was generally consistent across fibrosis stages.

For patients with **genotype 1** chronic hepatitis C who are **treatment-naive** and non-cirrhotic, at a willingness to pay (λ) of $50,000 per QALY, PAR/RIT12 + OMB12 + DAS12 is likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-naive and cirrhotic, SOF12 + LDV12 is likely to be the most cost-effective option compared with PR alone. The analysis also suggests that for patients with genotype 1 CHC infection who are **treatment-experienced** and non-cirrhotic: at a willingness to pay of $50,000 per QALY, PAR/RIT12 + OMB12 + DAS12 is likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-experienced and cirrhotic, Si12 PR24-48 response-guided therapy (RGT) is likely to be the most cost-effective option followed by SOF12 + LDV12 + RBV12 compared with PR alone.

The results of the base-case analysis suggest that for each **genotype 2, genotype 3, and genotype 4** treatment naive population (non-cirrhotic and cirrhotic), the interferon-free or the PR-based direct–acting antiviral (DAA) therapies appear not to be economically attractive compared with PR alone. At a willingness to pay of $50,000 per QALY, PR alone is still the most cost-effective for these populations and is generally consistent across fibrosis stages.

The analysis also suggests that for each genotype 2, genotype 3, and genotype 4 treatment-experienced population (non-cirrhotic and cirrhotic), there are interferon-free or the PR-based DAAs therapies that appear to be attractive at a willingness to pay of $50,000 per QALY when compared with no treatment.

For patients with **genotype 2** CHC infection who are treatment-experienced and non-cirrhotic, SOF12 + RBV12 is likely to be the most cost-effective option. For patients with genotype 2 CHC infection who are treatment-experienced and cirrhotic, So12 PR12 is likely to be the most cost-effective option**.** For patients with **genotype 3** CHC infection who are treatment-experienced and non-cirrhotic, So12 PR12 is likely to be the most cost-effective option. For patients with genotype 3 CHC infection who are treatment-experienced and cirrhotic, So12 PR12 is likely to be the most cost-effective option. Lastly, for patients with **genotype 4** CHC infection who are treatment-experienced, SOF24 + RBV24 is likely to be the most cost-effective option.
In the analyses that were stratified by fibrosis stage, ICURs for the interferon-free regimens compared with PR alone tended to be lower (more cost-effective) in patients with advanced fibrosis (F3) compared with patients with no or mild fibrosis (F0 to F2).

Extensive sensitivity analyses were conducted around the model input parameters, and the structural uncertainty was tested. Besides treatment efficacy, the main factors affecting the cost-effectiveness of the new interferon-free or the PR-based DAAs regimens versus PR alone were baseline age and the cost of antiviral therapies. The analyses showed that ICURs of new interferon-free or the PR-based DAAs therapies compared with PR tended to be lower (i.e., new interferon-free or the PR-based DAAs are more cost-effective) in younger patients. Additionally, the sensitivity analyses also showed that the cost-effectiveness results are highly sensitive to drug acquisition costs.

Results of both the multiple one-way sensitivity analyses and probabilistic sensitivity analysis provide evidence that PAR/RIT12 + OMB12 + DAS12 is likely to remain cost-effective despite the uncertainty of the model's parameters for genotype 1 treatment-naive non-cirrhotic patients; SOF12 + LDV12 is likely to remain cost-effective for genotype 1 treatment-naive patients with cirrhosis; PAR/RIT12 + OMB12 + DAS12 is likely to remain cost-effective parameters for genotype 1 treatment-experienced non-cirrhotic patients. However, due to the wide confidence intervals in the efficacy data for genotype 1 treatment-experienced patients with cirrhosis, the conclusions are uncertain.

The sensitivity analyses also suggested that PR is likely to remain the most cost-effective at a willingness to pay threshold of $50,000 per QALY for genotype 2, genotype 3, and genotype 4 treatment naive population (non-cirrhotic and cirrhotic). For genotype 2 treatment-experienced non-cirrhotic patients, SOF12 + RBV12 is likely to remain cost-effective when compared with no treatment; for genotype 2 treatment-experienced patients with cirrhosis, So12 PR12 RBV12 is likely to remain cost-effective when compared with no treatment. For genotype 3 treatment-experienced patients (non-cirrhotic and cirrhotic), So12 PR12 is likely to remain cost-effective when compared with no treatment.

Conclusions and Implications for Decision- or Policy-Making

The pharmacoeconomic analysis suggests that, for each genotype 1 population (treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic or treatment-experienced cirrhotic), at least one of the new interferon-free therapies appears to be economically attractive compared with PR alone. The drug that is the most cost-effective varies by population, but was generally consistent across fibrosis stages.

The pharmacoeconomic analysis also suggests that, for each genotype 2, genotype 3, and genotype 4 treatment naive population (non-cirrhotic and cirrhotic), the new interferon-free or the PR-based DAAs therapies appears not to be economically attractive compared with PR alone. At willingness to pay threshold of $50,000/QALY, PR alone is still the most cost-effective

for these population, and is generally consistent across fibrosis stages. However, for each genotype 2, genotype 3, and genotype 4 treatment-experienced population (non-cirrhotic and cirrhotic), the new interferon-free or the PR-based DAAs therapies appears to be economically attractive compared with **no treatment**.

1 CONTEXT AND POLICY ISSUES

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.[1] 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.[2] Chronic hepatitis C (CHC)-infected persons progress through various stages of disease and in due course may develop critical illnesses resulting from associated sequelae.[2,3] 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.[4,5]

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.[6,7] 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.[7,8] 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).[9] 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.[10,11]

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.[12] Based on this review, the Canadian Drug Expert Committee (CDEC) recommended that:[13]

- 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-naïve 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.

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.[14] 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.[15,16] 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 co-infection, decompensated liver disease, and liver transplant.

Regulatory approvals of newer regimens 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, CADTH has updated its previous Therapeutic Review to include recently approved and emerging regimens for the treatment of CHC infection (genotypes 1 through 6). Further information on the specific policy questions can be found in the accompanying Clinical Review report.

1.1 Objectives of the Report

To evaluate the cost effectiveness of treatment regimens for CHC infection (genotypes 1 through 4). While the scope of the Therapeutic Review update also encompasses genotypes 5 and 6, it was anticipated that there would be insufficient data to model cost effectiveness for these populations.

2 RESEARCH QUESTIONS

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

3 METHODS

3.1 Systematic Review

As part of the update to CADTH's therapeutic review of drugs for CHC infection, a systematic review and network meta-analysis were undertaken to evaluate the comparative efficacy and safety of regimens of interest. The methods and results for this review are presented in the accompanying Clinical Review report.

3.1.1 Type of Economic Evaluation

The analysis was in the form of a cost-utility analysis. The primary outcome was the number of quality-adjusted life-years (QALYs), with treatments compared by incremental cost per QALY (incremental cost-utility ratio [ICUR]).

3.1.2 Target Population

In the pharmacoeconomic analysis, the target population was Canadians infected with genotype 1, 2, 3 and 4 CHC infection. According to Statistics Canada, the prevalence of CHC infection is higher for age group 50 to 79.[4] Thus, for the baseline analysis, 50-year-old individuals infected with genotype 1, 2, 3 and 4 CHC infection were considered. A broader age range (40 to 60 years) was considered in the sensitivity analyses. Patients' weight was assumed to be 80 kg, which was consistent with previous therapeutic review.[12]

Due to limited availability of published data, the analysis avoided placing implicit proportion assumptions on the treatment population where possible. In the analysis, cohorts were defined by age, treatment status (naive versus experienced), and cirrhotic status (non-cirrhotic versus cirrhotic). For some analyses, distribution of fibrosis stages of the target population was needed. In the absence of estimates in the general CHC infected population, the distribution of fibrosis stages among patients with CHC infection was estimated using Canadian data from clinical practice settings (Table 1).[17,18] Sensitivity analyses in which the proportions varied by ± 25% were applied to determine whether these distribution estimates had a significant impact on the results.

Table 1: Fibrosis Distribution

Treatment Status and Fibrosis Stage	Base Estimate	Lower Limit (–25%)	Upper Limit (+25%)	Probability Distribution
Treatment-Naive[17]				
F0	0.08	0.06	0.1	Beta (58.8,676.2)
F1	0.20	0.15	0.25	Beta (51,204)
F2	0.35	0.2625	0.4375	Beta (41.25,76.61)
F3	0.21	0.1575	0.2625	Beta (50.35,189.41)
F4	0.16	0.12	0.2	Beta (53.6,281.4)
Treatment-Experienced[18]				
F0	0.04[a]	0.03	0.05	Beta (61.4,1473.6)
F1	0.13[a]	0.0975	0.1625	Beta (55.55,371.76)
F2	0.38[a]	0.285	0.475	Beta (39.3,64.12)
F3	0.23	0.1725	0.2875	Beta (49.05,164.21)
F4	0.22	0.165	0.275	Beta (49.7,176.2)

F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis.
[a]The original publication provided only an aggregate estimate for F0 to F2 (55%). Individual rates were extrapolated and validated by clinical experts.

3.1.3 Treatments

The main treatment regimens of interest for the updated Therapeutic 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 or US clinical practice guidelines; 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.

For the assessment of cost effectiveness, publicly available prices were required for regimens of interest to be included in the primary analysis (Table 2). Exploratory analyses were conducted to incorporate daclatasvir and asuneprevir based regimens in cost effectiveness analyses; both agents had been submitted to the Common Drug Review (CDR) as pre-NOC submissions at the time of analysis, however prices were not provided by the manufacturer upon request.

Table 2: Available Treatments Included in Primary Analysis

Treatment Comparators	Description
Genotype 1 Naive Non-cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
(5) SIM12 + SOF12	simeprevir + sofosbuvir for 12 weeks
(6) SOF12 + LDV12	sofosbuvir + ledipasvir for 12 weeks
(14) PAR/RIT12 + OMB12 + DAS12	paritaprevir/ritonavir + ombitasvir + dasabuvir for 12 weeks
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks
(32) T12 PR24-48 RGT q8	telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks (750 mg every 8 h)
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
(41) So12 PR24-48 RGT	sofosbuvir for 12 weeks and PR used as RGT for 24 or 48 weeks
(42) Si12 PR24-48 RGT	simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks
(46) B24 PR28-48 RGT	boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks
(72) SOF12+ SIM12+RBV12	simeprevir + sofosbuvir+ ribavirin for 12 weeks
Genotype 1 Naive cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
(5) SIM12 + SOF12	simeprevir + sofosbuvir for 12 weeks
(6) SOF12 + LDV12	sofosbuvir + ledipasvir for 12 weeks
(32) T12 PR24-48 RGT q8	telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks (750 mg every 8 h)
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
(42) Si12 PR24-48 RGT	simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks
(46) B24 PR28-48 RGT	boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks
Genotype 1 Experienced Non-cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(5) SIM12 + SOF12	simeprevir + sofosbuvir for 12 weeks
(6) SOF12 + LDV12	sofosbuvir + ledipasvir for 12 weeks
(14) PAR/RIT12 + OMB12 + DAS12	paritaprevir/ritonavir + ombitasvir + dasabuvir for 12 weeks

Table 2: Available Treatments Included in Primary Analysis	
Treatment Comparators	**Description**
Genotype 1 Naive Non-cirrhotic	
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks
(39) T12 PR48 q8	telaprevir for 12 weeks and PR for 48 weeks (750 mg every 8 h)
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
(42) Si12 PR24-48 RGT	simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks
(68) Si12 PR48	simeprevir for 12 weeks and PR for 48 weeks
(72) SOF12+ SIM12+RBV12	simeprevir + sofosbuvir+ ribavirin for 12 weeks
(74) B32 PR36-48 RGT	boceprevir for 32 weeks and PR used as RGT for 36 or 48 weeks
Genotype 1 Experienced cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(5) SIM12 + SOF12	simeprevir + sofosbuvir for 12 weeks
(7) SOF24 + LDV24	sofosbuvir + ledipasvir for 24 weeks
(10) SOF12 + LDV12 + RBV12	sofosbuvir + ledipasvir + ribavirin for 12 weeks
(39) T12 PR48 q8	telaprevir for 12 weeks and PR for 48 weeks (750 mg every 8 h)
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
(42) Si12 PR24-48 RGT	simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks
(68) Si12 PR48	simeprevir for 12 weeks and PR for 48 weeks
(74) B32 PR36-48 RGT	boceprevir for 32 weeks and PR used as RGT for 36 or 48 weeks
Genotype 2 Naive Non-cirrhotic	
(3) SOF12 + RBV12	sofosbuvir + ribavirin for 12 weeks
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
(70) PR24	pegylated interferon + ribavirin for 24 weeks
Genotype 2 Naive Cirrhotic	
(3) SOF12 + RBV12	sofosbuvir + ribavirin for 12 weeks
(70) PR24	pegylated interferon + ribavirin for 24 weeks
Genotype 2 Experienced Non-cirrhotic	
(3) SOF12 + RBV12	sofosbuvir + ribavirin for 12 weeks
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
Genotype 2 Experienced Cirrhotic	
(3) SOF12 + RBV12	sofosbuvir + ribavirin for 12 weeks
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
(73) SOF16 + RBV16	sofosbuvir + ribavirin for 16 weeks
Genotype 3 Naive Non-cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
Genotype 3 Naive cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks

Table 2: Available Treatments Included in Primary Analysis	
Treatment Comparators	**Description**
Genotype 1 Naive Non-cirrhotic	
Genotype 3 Experienced non-cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
Genotype 3 Experienced Cirrhotic	
(1) PR48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
(40) So12 PR12	sofosbuvir + pegylated interferon + ribavirin for 12 weeks
Genotype 4 Naive Non-cirrhotic	
(1) PR 48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
Genotype 4 Naive Cirrhotic	
(1) PR 48	pegylated interferon + ribavirin for 48 weeks
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
Genotype 4 Experienced Non-cirrhotic	
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks
Genotype 4 Experienced Cirrhotic	
(4) SOF24 + RBV24	sofosbuvir + ribavirin for 24 weeks

3.1.4 Perspective

This analysis was conducted from the perspective of a provincial Ministry of Health in Canada.

3.1.5 Time Horizon

The analysis adopted a lifetime horizon with a weekly cycle length. According to the modelling good research practices developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in collaboration with the Society for Medical Decision-Making (SMDM), the cycle length should be short enough to represent the frequency of clinical events and interventions.[19] In the case of hepatitis C, clinical events such as adverse events, duration of treatment, and SVR occur in a weekly manner; thus, a weekly cycle was used in the economic model. Future costs and health benefits were discounted at 5% annually.

3.1.6 Model Structure

In the analysis, a state-transition model based on the previous therapeutic review[12] was implemented using TreeAge Pro 2014 software.[20] The model was divided into a treatment module and a natural history module. The treatment module could easily be modified to reflect different treatment algorithms, whereas the natural history module was a robust model that reflected the natural history of CHC infection and was validated against other models in the literature. In the model, health states related to treatment and adverse events, fibrosis stages

(F0 to F4), and clinical states (e.g., cirrhosis, hepatocellular carcinoma) were used to reflect the natural history of CHC infection (Table 3).

Table 3: Description of Health States

Health States	Description
F0	No fibrosis; currently on treatment
F1	Portal fibrosis without septa; currently on treatment
F2	Portal fibrosis with rare septa; currently on treatment
F3	Numerous septa without cirrhosis; currently on treatment
F4	Cirrhosis; currently on treatment
F0 non-SVR	No fibrosis; failure to achieve SVR after treatment
F1 non-SVR	Portal fibrosis without septa; failure to achieve SVR after treatment
F2 non-SVR	Portal fibrosis with rare septa; failure to achieve SVR after treatment
F3 non-SVR	Numerous septa without cirrhosis; failure to achieve SVR after treatment
F4 non-SVR	Cirrhosis; failure to achieve SVR after treatment
F0 SVR	No fibrosis; achieved SVR after treatment
F1 SVR	Portal fibrosis without septa; achieved SVR after treatment
F2 SVR	Portal fibrosis with rare septa; achieved SVR after treatment
F3 SVR	Numerous septa without cirrhosis; achieved SVR after treatment
F4 SVR	Cirrhosis; achieved SVR after treatment
Decompensated cirrhosis	Decompensated cirrhosis
HCC	Hepatocellular carcinoma
Liver transplant	First year after liver transplant
Post-transplant	After first year of liver transplant
Liver-related death	Liver-related death related to decompensated cirrhosis, HCC, or liver transplant
All-cause death	All causes of death

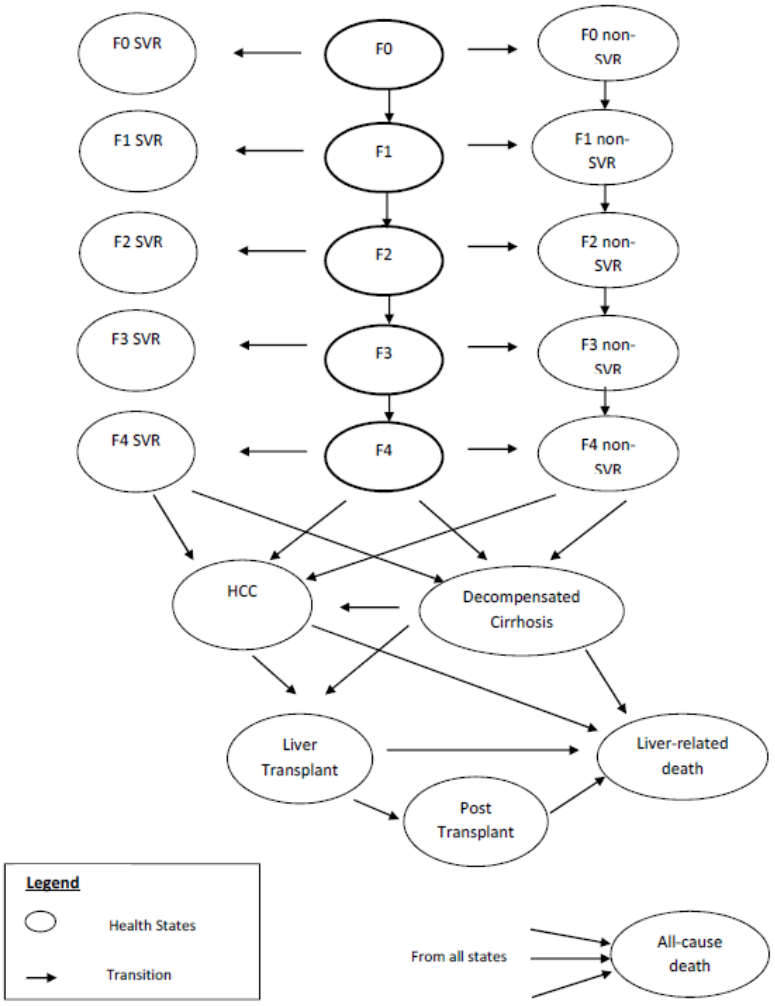
HCC = hepatocellular carcinoma; SVR = sustained virologic response.

During simulation, cohort members move between pre-defined health states in weekly cycles until all members have died. Health states and allowed transitions among health states are shown in Figure 1.

In this model, CHC-infected individuals with fibrosis stages F0 to F3 are initially assumed to have no cirrhosis, but progress over time to different clinical states of CHC infection, or development of cirrhosis, or both. Those developing cirrhosis may develop decompensated liver disease, hepatocellular carcinoma (HCC), or both, and may die from the complications of liver disease or require a liver transplant.

When simulation was initiated, cohort members were distributed into health states according to different levels of fibrosis, based on Table 1. The cohort members received one of the treatment regimens depending on patient characteristics (genotype, experience with treatment), Table 2. Probability of achieving SVR, all-cause treatment discontinuations, and three different types of adverse events (anemia, depression, and rash) were based on information from the clinical review. After treatment, cohort members were classified into SVR group or non-SVR group. The model assumed that non-cirrhotic patents who achieved SVR would not further progress into advanced liver disease, while patients with cirrhosis who achieved SVR will progress into advanced liver disease in a lowered rate. For those patients who did not achieved SVR, the model assumed that they will progress over time to different clinical states of CHC infection and/or cirrhosis based on the natural history progression.

Figure 1: State-Transition Model of Hepatitis C Virus Infection and Progression



F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; HCC = hepatocellular carcinoma; SVR = sustained virologic response.

3.1.7 Data Inputs

Data inputs are subject to uncertainty regarding their true value, known as parameter uncertainty.[21] Parameter uncertainty can be assessed by implementing an informal Bayesian approach to cost-effectiveness analysis by specifying relevant parameters as probability distributions rather than point estimates. This technique allows for the estimation of the likelihood of various output values based on a wide number of sets of input parameters generated by sampling from their probability density functions and was implemented in the probabilistic sensitivity analysis.

a) Natural History of the Disease

Fibrosis progression parameters were obtained from a systematic review conducted by Thein et al. in 2008,[22] which estimated the annual transition probabilities between fibrosis stages from 111 prognostic studies with 33,121 patients.[22] The progression parameters were derived from all published literature around the world from 1990 to 2007, the majority of which assessed liver

clinic populations (84%). Although there is likely some uncertainty regarding the true transition rates, these rates are the most robust currently available in the literature and were acceptable to the clinical experts. For genotype 3 analysis, the model assumed an accelerated fibrosis progression with an odds ratio of 1.52.[23]

Transition probabilities to advanced liver disease were obtained from a published study that provided separate estimates for both SVR and non-SVR among CHC infected patients.[24] Annual probabilities for fibrosis progression and advanced disease progression are provided in Table 4.

Table 4: Natural History Parameters

Description	Base Estimate	Lower Limit (95% CI)	Upper Limit (95% CI)	Probability Distribution
Annual Probability for Fibrosis Progression				
F0 → F1[22]	0.117	0.104	0.13	Beta (285.9,2158.3)
F1 → F2[22]	0.085	0.075	0.096	Beta (218.5,2351.6)
F2 → F3[22]	0.12	0.109	0.133	Beta (299.8,2198.6)
F3 → F4[22]	0.116	0.104	0.129	Beta (281.4,2144.7)
Genotype 3 accelerated fibrosis progression (OR)[23]	1.52	1.12	2.07	exp(Normal (0.419,0.154))
Annual Probability for Cirrhosis Progression				
F4 → decompensated (non-SVR)[24]	0.035	0.027	0.043	Beta (73.8,2036.1)
F4 → decompensated (SVR)[24]	0.002	0.0001	0.005	Beta (1.77,884.3)
F4 → HCC (non-SVR)[24]	0.024	0.018	0.031	Beta (45.9,1865.3)
F4 → HCC (SVR)[24]	0.005	0.001	0.009	Beta (6.21,1236.5)

CI = confidence interval; F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; HCC = hepatocellular carcinoma; SVR = sustained virologic response.

b) Treatment Efficacy and Safety

Efficacy

Table 5 summarizes the treatment efficacy data for the treatments.

The baseline probability of achieving SVR (see Table 2 for treatment regimen nomenclature) was generated directly from the NMA model. The baseline probability was calculated by using the mean log odds of the SVR rate in the baseline group averaged over all trials included in the NMA in which baseline was used.[25] The probability of achieving SVR in the DAA treatment groups was obtained by multiplying the relative risk obtained from the NMA for each treatment by the baseline probability of achieving SVR in the baseline group. Please refer to accompanying Clinical Review report for a description of the NMA methods.

Since fibrosis stage is a well-known predictor of response to treatment, the pharmacoeconomic model used the efficacy data from the NMA stratified by non-cirrhotic versus cirrhotic (F0 to F3 and F4).

Table 5: Treatment Efficacy (Sustained Virologic Response)

Description	Baseline[a]/ RR	Lower Limit (95% CrI)	Upper Limit (95% CrI)	Probability Distribution
Genotype 1 Treatment-Naive				
Non-cirrhosis				
Reference baseline	0.4913[a]	0.4359	0.5456	Based on NMA

Table 5: Treatment Efficacy (Sustained Virologic Response)				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Probability Distribution**
Genotype 1 Treatment-Naive				
(1) PR48				
(4) SOF24 + RBV24	1.634	1.288	1.899	Based on NMA
(5) SIM12 + SOF12	1.802	0.8004	2.186	Based on NMA
(6) SOF12 + LDV12	1.978	1.78	2.225	Based on NMA
(14) PAR/RIT12 + OMB12 + DAS12	1.932	1.337	2.211	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	1.944	1.748	2.18	Based on NMA
(32) T12 PR24-48 RGT q8	1.555	1.312	1.767	Based on NMA
(40) So12 PR12	1.769	1.278	2.065	Based on NMA
(41) So12 PR24-48 RGT	1.727	1.245	2.055	Based on NMA
(42) Si12 PR24-48 RGT	1.589	1.411	1.784	Based on NMA
(46) B24 PR28-48 RGT	1.538	1.268	1.777	Based on NMA
(72) SOF12+ SIM12+RBV12	1.766	0.8601	2.176	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.3958[a]	0.3092	0.4906	Based on NMA
(4) SOF24 + RBV24	1.757	0.6207	2.571	Based on NMA
(5) SIM12 + SOF12	2.175	0.9347	2.949	Based on NMA
(6) SOF12 + LDV12	2.408	1.893	3.089	Based on NMA
(32) T12 PR24-48 RGT q8	1.43	0.6368	2.195	Based on NMA
(40) So12 PR12	2.038	1.125	2.749	Based on NMA
(42) Si12 PR24-48 RGT	1.695	1.057	2.387	Based on NMA
(46) B24 PR28-48 RGT	0.6456	0.1609	1.653	Based on NMA
Genotype 1 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (1) PR48	0.2571 [a]	0.2242	0.292	Based on NMA
(5) SIM12 + SOF12	1.023	0.04915	3.635	Based on NMA
(6) SOF12 + LDV12	3.564	2.992	4.151	Based on NMA
(14) PAR/RIT12 + OMB12 + DAS12	3.753	3.204	4.329	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	3.818	3.345	4.387	Based on NMA
(39) T12 PR48 q8	3.038	2.405	3.633	Based on NMA
(40) So12 PR12	3.097	2.276	3.768	Based on NMA
(42) Si12 PR24-48 RGT	2.587	1.757	3.207	Based on NMA
(68) Si12 PR48	3.045	2.152	3.718	Based on NMA
(72) SOF12+ SIM12+RBV12	2.354	0.2271	3.878	Based on NMA

Table 5: Treatment Efficacy (Sustained Virologic Response)				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Probability Distribution**
Genotype 1 Treatment-Naive				
(74) B32 PR36-48 RGT	2.547	1.692	3.328	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.1691 [a]	0.1165	0.2334	Based on NMA
(5) SIM12 + SOF12	4.665	1.796	7.161	Based on NMA
(7) SOF24 + LDV24	4.503	1.603	7.215	Based on NMA
(10) SOF12 + LDV12 + RBV12	4.626	2.931	7.005	Based on NMA
(39) T12 PR48 q8	3.027	1.361	5.425	Based on NMA
(40) So12 PR12	2.944	0.3161	6.236	Based on NMA
(42) Si12 PR24-48 RGT	3.563	1.608	6.091	Based on NMA
(68) Si12 PR48	2.709	0.8918	5.319	Based on NMA
(74) B32 PR36-48 RGT	2.521	0.7132	5.623	Based on NMA
Genotype 2 Treatment-Naive				
Non-cirrhosis				
(3) SOF12 + RBV12	1.16	1.083	1.244	Based on NMA
(40) So12 PR12	1.148	0.4762	1.266	Based on NMA
Reference baseline (70) PR24	0.8191[a]	0.7687	0.8619	Based on NMA
Cirrhosis				
(3) SOF12 + RBV12	1.375	1.026	1.791	Based on NMA
Reference baseline (70) PR24	0.6209[a]	0.4966	0.7344	Based on NMA
Genotype 2 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (3) SOF12 + RBV12	0.9549[a]	0.9071	0.9829	Based on NMA
(40) So12 PR12	1.006	0.8914	1.071	Based on NMA
Cirrhosis				
Reference baseline (3) SOF12 + RBV12	0.7331[a]	0.579	0.8554	Based on NMA
(40) So12 PR12	1.286	0.9865	1.643	Based on NMA
(73) SOF16 + RBV16	1.052	0.7123	1.414	Based on NMA
Genotype 3 Treatment-Naive				
Non-cirrhosis				
Reference baseline (1) PR48	0.7051[a]	0.6393	0.765	Based on NMA
(4) SOF24 + RBV24	1.318	1.177	1.47	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.6021[a]	0.5584	0.6441	Based on NMA
(4) SOF24 + RBV24	1.509	1.142	1.702	Based on NMA
Genotype 3 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (1) PR48	0.6082[a]	0.5786	0.6374	Based on NMA
(4) SOF24 + RBV24	1.467	1.315	1.591	Based on NMA

Table 5: Treatment Efficacy (Sustained Virologic Response)				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Probability Distribution**
Genotype 1 Treatment-Naive				
(40) So12 PR12	1.384	0.8798	1.62	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.4777[a]	0.4382	0.5174	Based on NMA
(4) SOF24 + RBV24	1.465	1.139	1.789	Based on NMA
(40) So12 PR12	1.731	1.09	2.086	Based on NMA
Genotype 4 Treatment-Naive				
Non-cirrhosis				
Reference baseline (1) PR48	0.65[a]	0.6266	0.6733	Based on NMA
(3) SOF12 + RBV12	1.166	0.1602	1.521	Based on NMA
(4) SOF24 + RBV24	1.276	0.8713	1.471	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.3804[a]	0.3567	0.4052	Based on NMA
(3) SOF12 + RBV12	0.7489	0.01985	2.461	Based on NMA
(4) SOF24 + RBV24	2.27	1.361	2.65	Based on NMA
Genotype 4 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (3) SOF12 + RBV12	0.6345[a]	0.4483	0.7983	Based on NMA
(4) SOF24 + RBV24	1.28	0.6814	1.905	Based on NMA
Cirrhosis				
Reference baseline (3) SOF12 + RBV12	0.5628[a]	0.2422	0.8484	Based on NMA
(4) SOF24 + RBV24	1.469	0.5728	3.505	Based on NMA

[a] Baseline probability. RR = relative risk. Refer to Table 2 for treatment description.

Safety

In the economic model, three different types of adverse events were considered: anemia, depression, and rash. These three adverse events were considered relevant for inclusion given clinical experts feedback and as they are associated with health care costs. The rates of adverse events obtained from the NMA (Table 6).

The baseline probability of experiencing the adverse event of interest in the baseline group (PR48) was generated directly from the NMA model. The baseline probability was calculated by using the mean log odds of the rate of each adverse event in the PR48 group averaged over all trials included in the NMA in which PR48 was used.[25] The probability of experiencing the adverse event in the DAA treatment groups was obtained by multiplying the relative risk obtained from the NMA for each treatment by the probability in the PR48 group.

Table 6: Adverse Events				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Probability Distribution**
Treatment-Naive				
Depression				
Reference baseline (1) PR48	0.1381[a]	0.11	0.1683	Based on NMA
(3) SOF12 + RBV12	0.2861	0.07992	0.958	Based on NMA
(4) SOF24 + RBV24	0.7751	0.165	3.181	Based on NMA
(5) SIM12 + SOF12	0.4174	0.08099	1.534	Assume same as (14)
(6) SOF12 + LDV12	0.01888	0.002205	0.09946	Based on NMA
(14) PAR/RIT12 + OMB12 + DAS12	0.4174	0.08099	1.534	Assume same as (15)
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.4174	0.08099	1.534	Based on NMA
(32) T12 PR24-48 RGT q8	0.8187	0.35	1.872	Based on NMA
(40) So12 PR12	0.5715	0.2133	1.531	Based on NMA
(41) So12 PR24-48 RGT	0.9319	0.1889	3.359	Based on NMA
(42) Si12 PR24-48 RGT	0.7241	0.4215	1.283	Based on NMA
(46) B24 PR28-48 RGT	1.038	0.4271	2.241	Based on NMA
(70) PR24	0.756	0.1592	2.831	Based on NMA
(72) SOF12+ SIM12+RBV12	0.4174	0.08099	1.534	Assume same as (15)
Anemia				
Reference baseline (1) PR48	0.2136[a]	0.1838	0.2459	Based on NMA
(3) SOF12 + RBV12	0.6949	0.3601	1.309	Based on NMA
(4) SOF24 + RBV24	1.263	0.4806	2.528	Based on NMA
(5) SIM12 + SOF12	0.3454	0.1431	0.7469	Assume same as (14)
(6) SOF12 + LDV12	0.05568	0.02193	0.1322	Based on NMA
(14) PAR/RIT12 + OMB12 + DAS12	0.3454	0.1431	0.7469	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.3826	0.1549	0.8366	Based on NMA
(32) T12 PR24-48 RGT q8	1.872	1.316	2.496	Based on NMA
(40) So12 PR12	1.487	0.8038	2.449	Based on NMA
(41) So12 PR24-48 RGT	0.8758	0.4101	1.728	Based on NMA
(42) Si12 PR24-48 RGT	0.8232	0.5901	1.118	Based on NMA
(46) B24 PR28-48 RGT	1.815	1.266	2.439	Based on NMA
(70) PR24	0.9708	0.4121	2.065	Based on NMA
(72) SOF12+ SIM12+RBV12	0.3826	0.1549	0.8366	Assume same as (15)
Rash				
Reference baseline (1) PR48	0.1828[a]	0.1465	0.2186	Based on NMA
(3) SOF12 + RBV12	0.5244	0.167	1.598	Based on NMA
(4) SOF24 + RBV24	0.7655	0.07902	2.721	Based on NMA
(5) SIM12 + SOF12	0.077192[a]	0.005312	0.502889	Assume same as experienced patients
(6) SOF12 + LDV12	0.2626	0.1415	0.4803	Based on NMA

Table 6: Adverse Events				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Probability Distribution**
(14) PAR/RIT12 + OMB12 + DAS12	0.2194	0.08837	0.525	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.7214	0.3777	1.301	Based on NMA
(32) T12 PR24-48 RGT q8	1.578	1.038	2.262	Based on NMA
(40) So12 PR12	0.8014	0.3667	1.771	Based on NMA
(41) So12 PR24-48 RGT	1.597	0.7911	2.955	Based on NMA
(42) Si12 PR24-48 RGT	1.117	0.8079	1.519	Based on NMA
(46) B24 PR28-48 RGT	1.11	0.6968	1.682	Based on NMA
(70) PR24	1.03	0.3068	2.839	Based on NMA
(72) SOF12+ SIM12+RBV12	0.237167[a]	0.047817	0.634031	Assume same as experienced patients
Treatment-Experienced				
Depression				
Reference baseline (1) PR48	0.1318	0.09864	0.1697	Based on NMA
(3) SOF12 + RBV12	0.4582	0.1368	1.314	Based on NMA
(5) SIM12 + SOF12	0.2691	0.06677	0.9281	Assume same as (14)
(6) SOF12 + LDV12	0.002607[a]	0.000305	0.013735	Assume same as Naive patients
(7) SOF24 + LDV24	0.002607[a]	0.000305	0.013735	Assume same as (6)
(10) SOF12 + LDV12 + RBV12	0.6401	0.2198	1.648	Based on NMA
(14) PAR/RIT12 + OMB12 + DAS12	0.2691	0.06677	0.9281	Assume same as (15)
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.2691	0.06677	0.9281	Based on NMA
(39) T12 PR48 q8	0.6684	0.3521	1.264	Based on NMA
(40) So12 PR12	0.078924[a]	0.029457	0.211431	Assume same as Naive patients
(42) Si12 PR24-48 RGT	0.099998[a]	0.058209	0.177182	Assume same as Naive patients
(68) Si12 PR48	0.912	0.4586	1.765	Based on NMA
(72) SOF12+ SIM12+RBV12	0.2691	0.06677	0.9281	Assume same as (15)
(73) SOF16 + RBV16	0.4582	0.1368	1.314	Assume same as (3)
(74) B32 PR36-48 RGT	0.9477	0.4244	1.986	Based on NMA
Anemia				
Reference baseline (1) PR48	0.1901	0.1625	0.2202	Based on NMA
(3) SOF12 + RBV12	0.6957	0.2952	1.605	Based on NMA
(5) SIM12 + SOF12	0.009479	7.65E-04	0.07197	Assume same as (14)
(6) SOF12 + LDV12	0.02436	0.00283	0.1074	Based on NMA
(7) SOF24 + LDV24	0.02436	0.00283	0.1074	Assume same as (6)
(10) SOF12 + LDV12 + RBV12	0.3139	0.1473	0.5881	Based on NMA

Table 6: Adverse Events				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Probability Distribution**
(14) PAR/RIT12 + OMB12 + DAS12	0.009479	7.65E-04	0.07197	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.2731	0.1146	0.6623	Based on NMA
(39) T12 PR48 q8	1.944	1.313	2.792	Based on NMA
(40) So12 PR12	1.016	0.5612	1.692	Based on NMA
(42) Si12 PR24-48 RGT	0.8345	0.4458	1.478	Based on NMA
(68) Si12 PR48	0.6838	0.3979	1.167	Based on NMA
(72) SOF12+ SIM12+RBV12	0.2731	0.1146	0.6623	Assume same as (15)
(73) SOF16 + RBV16	0.6957	0.2952	1.605	Assume same as (3)
(74) B32 PR36-48 RGT	2.402	1.547	3.593	Based on NMA
Rash				
Reference baseline (1) PR48	0.1322	0.1071	0.1594	Based on NMA
(3) SOF12 + RBV12	1.112	0.3782	2.734	Based on NMA
(5) SIM12 + SOF12	0.5839	0.04018	3.804	Based on NMA
(6) SOF12 + LDV12	0.1656	0.04229	0.5608	Based on NMA
(7) SOF24 + LDV24	0.1656	0.04229	0.5608	Assume same as (6)
(10) SOF12 + LDV12 + RBV12	0.6445	0.3272	1.316	Based on NMA
(14) PAR/RIT12 + OMB12 + DAS12	0.05563	0.003309	0.3552	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.6094	0.2367	1.812	Based on NMA
(39) T12 PR48 q8	2.216	1.401	3.796	Based on NMA
(40) So12 PR12	1.39	0.6411	2.806	Based on NMA
(42) Si12 PR24-48 RGT	1.019	0.444	2.121	Based on NMA
(68) Si12 PR48	1.44	0.8209	2.581	Based on NMA
(72) SOF12+ SIM12+RBV12	1.794	0.3617	4.796	Based on NMA
(73) SOF16 + RBV16	1.112	0.3782	2.734	Assume same as (3)
(74) B32 PR36-48 RGT	2.194	1.066	3.943	Based on NMA

[a] Baseline probability. RR = relative risk. Refer to Table 2 for treatment description.

All-Cause Treatment Discontinuation

In the economic model, all-cause treatment discontinuations were also considered (Table 7), and their rates from the studies included in the NMA were used to populate the model. Where possible, pooled estimates and 95% confidence intervals were calculated using a random effects model. It was assumed that patients who discontinued treatment would not to achieve SVR. In addition, detailed data on timing of treatment discontinuation were not routinely reported in published clinical data. Therefore, the model assumed that the discontinuation occurred in the middle of the scheduled therapy (i.e., only half of the scheduled treatment costs were considered for the discontinued patients).

Table 7: Discontinuation Rate				
Description	**Base Estimate**	**Lower Limit (95% CI)**	**Upper Limit (95% CI)**	**Probability Distribution/ Note**
Treatment-Naive				
(1) PR48	0.173	0.096	0.292	Beta(6.818,32.594)
(3) SOF12 + RBV12	0.089	0.038	0.194	Beta(2.529,25.887)
(4) SOF24 + RBV24	0.054	0.015	0.180	Beta(0.641,11.23)
(5) SIM12 + SOF12	0.033	0.002	0.366	Beta(0.005,0.146) / Assume same as experienced patients
(6) SOF12 + LDV12	0.044	0.023	0.083	Beta(4.823,104.799)
(14) PAR/RIT12 + OMB12 + DAS12	0.005	0.001	0.033	Beta(0.122,24.261)
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.015	0.003	0.071	Beta(0.268,17.578)
(32) T12 PR24-48 RGT q8	0.092	0.074	0.114	Beta(63.423,625.957)
(40) So12 PR12	0.108	0.082	0.142	Beta(35.893,296.45)
(41) So12 PR24-48 RGT	0.106	0.045	0.231	Beta(2.466,20.794)
(42) Si12 PR24-48 RGT	0.070	0.052	0.093	Beta(34.387,456.862)
(46) B24 PR28-48 RGT	0.212	0.173	0.257	Beta(69.745,259.242)
(70) PR24	0.165	0.096	0.269	Beta(8.242,41.71)
(72) SOF12+ SIM12+RBV12	0.018	0.001	0.230	Beta(0.01,0.563) / Assume same as experienced patients
Treatment-Experienced				
(1) PR48	0.114	0.077	0.166	Beta(16.919,131.495)
(3) SOF12 + RBV12	0.081	0.004	0.684	Beta(0.002,0.023)
(5) SIM12 + SOF12	0.033	0.002	0.366	Beta(0.005,0.146)
(6) SOF12 + LDV12	0.017	0.003	0.079	Beta(0.279,16.111)
(7) SOF24 + LDV24	0.006	0	0.094	Beta(0.012,2.068)
(10) SOF12 + LDV12 + RBV12	0.016	0.005	0.049	Beta(0.909,55.92)
(14) PAR/RIT12 + OMB12 + DAS12	0.005	0.000	0.078	Beta(0.014,2.721)
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	0.015	0.003	0.071	Beta(0.268,17.578) / Assumed same as naive patients
(39) T12 PR48 q8	0.077	0.059	0.100	Beta(41.303,495.096)
(40) So12 PR12	0.006	0.000	0.091	Beta(0.014,2.288)
(42) Si12 PR24-48 RGT	0.038	0.021	0.070	Beta(5.388,136.409)
(68) Si12 PR48	0.059	0.040	0.085	Beta(19.323,308.191)
(72) SOF12+ SIM12+RBV12	0.018	0.001	0.230	Beta(0.01,0.563)
(73) SOF16 + RBV16	0.081	0.004	0.684	Assume same as (3)
(74) B32 PR36-48 RGT	0.099	0.061	0.155	Beta(11.165,101.61)

See Table 2 for treatment description.

Patients Eligible for Short-Duration Response-Guided Therapy

The proportion of the cohort eligible to receive shorter PR therapy based on RGT criteria was also considered in the analysis (Table 8), and was based on the previous therapeutic review.[12] Where possible, pooled estimates and 95% CI were calculated using a random effects model. The model assumed that eligible patients received shorter scheduled treatment duration and will account for a lowered therapy cost.

Table 8: Proportion of Cohort That Qualified for Short-Duration Response-Guided Therapy

Description	Base Estimate	Lower Limit (95% CI)	Upper Limit (95% CI)	Probability Distribution
Treatment-Naive				
(32) T12 PR24-48 RGT q8	0.647	0.598	0.693	Beta (245.53, 133.96)
(42) Si12 PR24-48 RGT	0.859	0.777	0.913	Beta (61.03,10.01)
(46) B24 PR28-48 RGT	0.44	0.39	0.491	Beta (166.29, 211.64)
Treatment-Experienced				
(42) Si12 PR24-48 RGT	0.927	0.888	0.953	Beta (164.05, 12.92)
(74) B32 PR36-48 RGT	0.457	0.382	0.534	Beta (76.05, 90.36)

Source: CADTH 2014.[12]

c) Mortality

In the absence of credible Canadian sources that would distinguish death from HCC and decompensated cirrhosis, data were obtained from sources estimated to be sufficiently generalizable to the Canadian population given the study's size and quality. More specifically, the annual mortality risks associated with advanced liver diseases were obtained from a US study based on cancer registries,[26] as well as a systematic review[27] (Table 9). All-cause mortality was obtained from Statistics Canada.[28]

Table 9: Chronic Hepatitis C–Related Mortality

Description	Base Estimate	Lower Limit (–25%)	Upper Limit (+25%)	Probability Distribution
HCC[26]	0.411	0.31	0.51	Beta (38.6, 55.3)
Decompensated cirrhosis[27]	0.216	0.162	0.27	Beta (49.96, 181.3)
Liver transplant (first year)[29]	0.142	0.124	0.159	Beta (213.4,1289.7)
Liver transplant (> 1 year)[29]	0.034	0.024	0.043	Beta (44.6,1268.1)

HCC = hepatocellular carcinoma.

d) Costs

The CHC infection-related costs were collected from a large Canadian costing study using administrative data (Table 10).[30] This study calculated the annual costs for three disease phases according to the natural history of CHC infection: early phase (before the diagnosis of HCC or decompensated cirrhosis or both), late phase (after the diagnosis of HCC or decompensated cirrhosis or both), and pre-death phase (the last 12 months before death). The annual costs for non-CHC infected individuals were also calculated and compared in the study. Costs included hospitalization, ambulatory care, long-term care, physician services, and diagnostic tests for 22,179 patients with CHC infection. The model assumed that when an individual achieved SVR, annual costs for non-CHC individuals would be applied. The liver transplant–related costs were collected from a Canadian costing study based on patient medical records obtained from hospitals.[31] All cost data were inflated to 2015 using the Statistics Canada Consumer Price Index for health care and personal items.

In the baseline analysis, the model used the related cost derived for individuals aged 45 to 54. A different cost range was considered in the sensitivity analyses.

Table 10: Chronic Hepatitis C–Related Cost

Description	Base Estimate	Lower Limit (–25%)	Upper Limit (+25%)	Probability Distribution
Annual Cost CHC infection Early Phase[30]				
Age 45 to 54 (base case)	$4,589	$4,498	$4,682	Gamma(9739.355,2.122)
Age 35 to 44 (SA)	$3,888	$3,812	$3,967	Gamma(9688.54,2.492)
Age 55 to 64 (SA)	$5,541	$5,377	$5,710	Gamma(4299.945,0.776)
Annual Cost CHC infection Late Phase[30]				
Age 45 to 54 (base case)	$14,597	$13,475	$15,812	Gamma(577.344,0.04)
Age 35 to 44 (SA)	$12,054	$11,582	$12,546	Gamma(2401,0.199)
Age 55 to 64 (SA)	$12,337	$11,619	$13,100	Gamma(1045.755,0.085)
Annual Cost CHC infection Pre-death Phase[30]				
Age 45 to 54 (base case)	$41,823	$39,388	$44,410	Gamma(1045.436,0.025)
Age 35 to 44 (SA)	$35,544	$32,811	$38,504	Gamma(576.779,0.016)
Age 55 to 64 (SA)	$52,102	$49,561	$54,773	Gamma(1522.022,0.029)
Annual Cost Non-CHC infection Before Pre-death Phase[30]				
Age 45 to 54 (base case)	$2,362	$2,338	$2,387	Gamma(35705.882,15.117)
Age 35 to 44 (SA)	$1,813	$1,777	$1,850	Gamma(9604,5.297)
Age 55 to 64 (SA)	$3,925	$3,809	$4,044	Gamma(4351.564,1.109)
Annual Cost Non-CHC infection Pre-death Phase[30]				
Age 45 to 54 (base case)	$45,207	$44,312	$46,120	Gamma(9806.856,0.217)
Age 35 to 44 (SA)	$42,291	$40,229	$44,459	Gamma(1522.08,0.036)
Age 55 to 64 (SA)	$44,542	$43,660	$45,442	Gamma(9797.48,0.22)
Transplant-related Costs				
Cost of transplant[31]	$120,593	$90,445	$150,741	Gamma (64,0.0033)
Annual cost of post-transplant follow-up care[31]	$19,400	$14,550	$24,250	Gamma (64,0.0005)

CHC = chronic hepatitis C. SA= sensitivity analysis

The costs of antiviral therapies (Table 11) were collected from: the Ontario Drug Benefit Exceptional Access Program (June 2015); Yukon Drug Formulary (March 2015); and the Saskatchewan Drug Benefit (March 2015). Since the cost of pegylated interferon and ribavirin depend on the patient's weight, the patient's weight was assumed to be 80 kg in the analysis, which was consistent with the previous therapeutic review.[12]

Newer treatments without price information were included in exploratory analyses by assuming the price of these regimens ranged between $55,860 (cost of PAR/RIT12 + OMB12 + DAS12) to $67,000 (cost of SOF12 + LDV12).

Table 11: Therapy Cost							
Drug	**Strength**	**Dosage Form**	**Price ($)**	**Recommended Dose**	**Duration**	**Cost For 1 Course of Therapy ($)**	**Cost for 1 Course of Combo Therapy ($)**
Interferon-Free Regimens							
PAR/RIT/OMB and DAS (Holkira Pak)	75/ 50/12.5mg 250 mg	Tab	$665.00 [b]	25/150/100 mg ombitasvir/ paritaprevir/ ritonavir once daily and 250 mg dasabuvir twice daily	12 weeks[a]	55,860	55,860
PAR/RIT/OMB and DAS plus RBV (Holkira Pak)	75/ 50/12.5 mg 250 mg	Tab	$665.00[b]	As above plus 1,000 to 1,200 mg/day RBV	12 to 24 weeks[a]	55,860 to 111,720	58,905 to 119,028
	400 mg 600 mg		14.5000[b] 21.7500[b]			3,045 to 7,308	
Ledipasvir / Sofosbuvir (Harvoni)	90/400 mg	Tab	797.62[c]	90/400 mg once daily	8 to 24 weeks[d]	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)	44,667 (8 weeks) 67,000 to 134,000 (12 to 24 weeks)
Direct-Acting Antivirals in Combination With Peginterferon Alpha Plus Ribavirin Therapy							
Sofosbuvir (Sovaldi) plus PegIFN/RBV	400 mg	Tab	654.76	400 mg once daily	12 weeks[e]	55,000	59,750
	180 mcg /200 mg	Vial/ Tabs	395.84	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day[g]	12 weeks	4,750	
Sofosbuvir (Sovaldi) plus RBV	400 mg	Tab	654.76	400 mg once daily	24 weeks	110,000	116,090 to 117,308
	400 mg 600 mg	Tab	14.50[c] 21.75[c]	1000 to 1200 mg daily	24 weeks	6,090 to 7,308	
Simeprevir (Galexos) plus PefIFN/RBV	150 mg	Cap	434.55	150 mg once daily	12 weeks	36,502	46,002 to 55,502
	180 mcg /200 mg	Vial/ Tabs	395.84[g]	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day	24 to 48 weeks	9,500 to 19,000	
Boceprevir (Victrelis) plus PegIFN/RBV	200 mg	Cap	12.50	4 x 200 mg three times daily	24 to 44 weeks	25,200 to 46,200	37,365 to 67,055
	120 mcg/200 mg	Pens/ Caps	868.96	PegIFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day	28 to 48 weeks	12,165 to 20,855	
Peginterferon Alpha Plus Ribavirin Therapy							
PegIFN alfa-2a plus RBV (Pegasys RBV)	180 mcg /200 mg	Vial or syringe/ 28 Tabs 35 Tabs 42 Tabs	395.84	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day[d]	24 to 48 weeks	9,500 to 19,000	9,500 to 19,000

Table 11: Therapy Cost							
Drug	**Strength**	**Dosage Form**	**Price ($)**	**Recommended Dose**	**Duration**	**Cost For 1 Course of Therapy ($)**	**Cost for 1 Course of Combo Therapy ($)**
PegIFN alfa-2b plus RBV (Pegetron)	50 mcg/200 mg	2 Vials + 56 Caps	786.39	PegIFN 1.5 mcg/kg/week; RBV 800 to 1,400 mg/day[d]	24 to 48 weeks	9,437 to 18,873	9,437 to 18,873
	150 mcg/200 mg	2 Vials + 84 or 98 Caps	868.96			10,428 to 20,855	10,428 to 20,855
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg	2 Pens / 56 to 98 Caps	786.39 786.39 868.96 868.96			9,437 to 20,855	9,437 to 20,855
Telaprevir (Incivek) plus PegIFN/RBV	375 mg	Tab	69.38	3 x 375 mg two times daily	12 weeks	34,968	44,468 to 53,968
	180 mcg /200 mg	Vial/ Tabs	395.84	PegIFN 180 mcg/week; RBV 800 to 1,200 mg/day[f]	24 to 48 weeks	9,500 to 19,000	
Boceprevir/ PegIFN alfa-2b/ RBV (Victrelis Triple)	200/80/200 200/100/200 200/120/200 200/150/200 (mg/mcg/mg)	168 Caps+ 2 Pens+ 56 Caps	2652.55[g] 2652.55[g] 2726.00[g] 2726.00[g]	Boceprevir 800 mg three times daily; PegIFN 1.5 mcg/kg/week; RBV 800 to 1,400 per day	24 to 44 weeks	31,831 to 59,972	31,831 to 59,972

IFN=Interferon, IM=intramuscular, IU=International unit, IV=intravenous, M=millions, mcg=micrograms, mL=millilitres, mg=milligrams, PegIFN=Peginterferon, RBV=Ribavirin
Source: Saskatchewan Drug Benefit (February 2015) prices unless otherwise stated.

[a] 12 weeks of OBV/PTV/RTV and DSV alone for patients with genotype 1b without cirrhosis; 12 weeks of OBV/PTV/RTV and DSV plus RBV for patients with genotype 1a without cirrhosis and genotype 1a and 1b with cirrhosis; 24 weeks of OBV/PTV/RTV and DSV plus RBV for patients with genotype 1a with cirrhosis who had previous null response to pegIFN and RBV. Price obtained from AbbVie website.

[b] Ontario Exceptional Access Program (June 29, 2015). Sofosbuvir in combination with ribavirin (as a stand-alone agent) for 24 weeks can be considered as a therapeutic option for treatment naive and non-cirrhotic treatment-experienced CHC infected patients with genotype 1 infection who are ineligible to receive an interferon-based regimen.

[c] Yukon Drug Formulary (March 2015) and Ontario Exceptional Access Program (March 24, 2015).

[d] 12 weeks for genotype 1 treatment-naive patients and treatment-experienced patients without cirrhosis; 24 weeks for treatment-experienced patients with cirrhosis. 8 weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment hepatitis C virus RNA less than 6 million IU/mL.

[e] 12 weeks for genotype 1, 2, 4; 16 to 24 weeks for genotype 3.

[f] Dosing varies by weight and HCV genotype.

[g] Ontario Drug Benefit Formulary (March 2015).

The cost of treating adverse events was based on resource utilization data reported in Gao et al.,[32] and the associated Canadian costs obtained from the literature. Specifically, Canadian costs were acquired from the Ontario Drug Benefit Formulary, the Schedule of Benefits for Laboratory Services in Ontario, and the Schedule of Benefits for Physician Services, Ontario. The cost of transfusion was based on the published literature,[33] and inflated to 2015 Canadian funds using the health care component of the Consumer Price Index.[12] The average per-event costs for anemia was $2,060.41, for depression was $981.11, and $255.90 for rash based on 48 weeks of treatment. The average per-event costs were adjusted by the corresponding treatment duration and applied to the economic model based on the rate of adverse event occurrence per treatment option.

e) Utilities

Utility information for health states were obtained from the most recent and valid Canadian utility study available using Health Utilities Index Mark 2 (HUI2).[34] The study included 700 patients across different CHC infection health states. Since the study did not include patients with decompensated cirrhosis, utility for these patients was determined by adjusting the CHC infection utility score from a disutility value published in a systematic review (Table 13).[35] The on-treatment utility and the viral clearance utility for CHC infected patients who had compensated cirrhosis was determined by adjusting the compensated cirrhosis utility score with a disutility value (–0.02) and a utility gain value (+0.07) for patients without cirrhosis. The utilities of CHC infected patients who had late-stage liver disease (decompensated cirrhosis or HCC) were obtained from a relatively small sample size and may not cover the full spectrum of the severity of the disease. In consultation with clinical experts, the utility value for HCC was assumed to be the same as compensated cirrhosis. A separate set of utility data was used in a sensitivity analysis (Chong et al.[36])(Appendix 1).

In the economic model, a general on-treatment disutility was applied during the treatment period for regimens containing pegylated interferon alfa (PEG) or RBV. In addition to the general on-treatment disutility, one-time disutility values associated with anemia, depression, and rash were applied for the patients experiencing the adverse event. In the absence of disutility data associated with adverse events in CHC infected patients, these disutilities were estimated using scores measured either in the general population, or in patients with treatment-induced anemia.[37,38]

The purpose of the general on-treatment disutility was to account for other adverse effects aside from anemia, depression, and rash. Note that there was a potential for double-counting in terms of disutility for patients who experienced anemia, depression, and rash. In the sensitivity analysis, we explored the effect of elimination of the additional disutility used for anemia, depression, and rash.

Table 12: Cost of Adverse Events Associated With Chronic Hepatitis C Therapies							
Event	**Resource Utilized**	**Utilization (%)**	**Frequency in Weeks (Number Used for the HE Model)**	**Cost/ Unit**	**Total Cost During Therapy[a]**	**Total Cost Per Patient**	**2015 Inflated Cost Per Patient[e]**
Anemia	Epoetin alfa 40,000 IU pre-filled syringe (Eprex)[b]	22	16	$432.67	$1,523.00	$2,048.29	$2,060.41
	Blood count — WBC differential (L393; 16 LSM units × $0.517)[c]	100	3	$8.27	$24.82		
	Bilirubin — total (L030; 5 LSM units $0.517)[c]	100	3 to 7 (3)	$2.59	$7.76		
	Uric acid (L252; 5 LSM units × $0.517)[c]	100	3 to 7 (3)	$2.59	$7.76		
	Reticulocytes (L398; 13 LSM units[a] × $0.517)[c]	100	3 to 7 (3)	$6.72	$20.16		
	Red blood cell transfusion	22	1 to 2 (1)	$334.27	$73.54		
	Clinic visit and injection (G373)[d]	22	16	$6.75	$23.76		
	Hematology consultation (A615)[d]	100	1 to 5 (1)	$157.00	$157.00		
	Repeat hematology consultation (A616)[d]	100	2 to 12 (2)	$105.25	$210.50		
Depression	210 mg citalopram/week[b]	7	48	$3.50	$11.74	$975.34	$981.11
	Individual outpatient psychotherapy (K197)[d]	100	(12)	$80.30	$963.60		
Rash	Hydrocortisone cream 1% (45 g)[b]	100	12 to 24 (12)	$7.73	$92.77	$254.39	$255.90
	Simple clinic visit (A005)[d]	100	2 to 4 (2)	$77.20	$154.40		
	Dermatology consultation (A025)[d]	5	2 to 4 (2)	$72.15	$7.22		

HE = health economic; IU = international units; LSM = labour, materials, supervision units. Each unit is worth $0.517.
WBC = white blood cells.
[a] Total cost = cost/unit × frequency × utilization.
[b] Ontario Drug Benefit Formulary (March 2014).
[c] Schedule of Benefits for Laboratory Services, Ontario (April 1, 1999).
[d] Schedule of Benefits for Physician Services, Ontario (October 1, 2013).
[e] Inflate to 2015 costs using the Statistics Canada Consumer Price Index for health care and personal items.

Table 13: Chronic Hepatitis C–Related Utilities				
Description	**Base Estimate**	**Lower Limit (–25%)**	**Upper Limit (+25%)**	**Probability Distribution**
Canadian Population Average[39]				
Age 45 to 54	0.86	0.83	0.88	Beta (459.34,74.78)
Utility for CHC infection–Related Health States[34]				
Non-cirrhosis	0.73	0.69	0.77	Beta (358.98,132.77)
Compensated cirrhosis	0.69	0.65	0.73	Beta (368.29,165.46)
HCC[a]	0.69	0.65	0.73	Beta (368.29,165.46)
Decompensated cirrhosis[35]	0.65	0.61	0.69	Beta (369.04,198.71)
Post-transplant	0.75	0.70	0.79	Beta (224.25,74.75)
Non-cirrhosis on-treatment (apply only to regimens contains PEG or RBV)	0.71	0.67	0.75	Beta (364.76,148.99)
Non-cirrhosis viral clearance	0.80	0.76	0.84	Beta (319.2,79.8)
Compensated cirrhosis on-treatment (apply only to regimens contains PEG or RBV)	0.67	0.63	0.71	Beta (369.67,182.08)
Compensated cirrhosis viral clearance	0.76	0.72	0.80	Beta (345.8,109.2)
One-time Disutility Associated With Adverse Event[37,38]				
Anemia	–0.03	–0.0375	–0.0225	–Beta (62.05,2006.28)
Depression	–0.0625	–0.0781	–0.0468	–Beta (59.94,899.06)
Rash	–0.0213	–0.0267	–0.0159	–Beta (62.62,2006.28)

CHC = chronic hepatitis C; HCC = hepatocellular carcinoma.
[a]Assume same as compensated cirrhosis.

3.1.8 Other Assumptions Within the Economic Model

The following assumptions were made for the economic model (Table 14).

Table 14: Other Assumptions Within the Economic Model

Description
• Appropriate to inflate costs to 2015 using the Statistics Canada Consumer Price Index for health care and personal items • HCC and decompensated cirrhosis were assumed to occur only at F4 • No switching on treatment was assumed • Patient populations in natural history studies were assumed to sufficiently reflect the Canadian population • AEs were assumed to be transient in nature and did not impact compliance • Model assumed no other pre-existing conditions; e.g., HIV • Model assumed no spontaneous remission • Patients who discontinued treatment were assumed not to achieve SVR • Patients who discontinued treatment did so in the middle of their scheduled therapy • Dosing and treatment duration based on the NMA results (in the base case) • Incidence of AEs is not affected by fibrosis stage and genotype

AE = adverse event; F4 = cirrhosis; HCC = hepatocellular carcinoma; NMA = network meta-analysis; SVR = sustained virologic response.

3.1.9 Exploratory Analyses

a) Exploratory Analyses for One-Time Reinfection

A recent systematic review reported an HCV reinfection rate of 2.4 per 100 person-years among active injection drug users (IDUs).[40] To measure the impact of one-time reinfection in the model in this exploratory analysis, the entire base-case analyses were re-run based on the following reinfection assumptions:

- The HCV reinfection rate was assumed to be 2.4 per 100 person-years.[40]
- The proportion of active IDU ranges between 5% (clinical opinion) and 21.7%.[1]
- Only one-time reinfection was considered.
- Once a patient is reinfected with HCV, the patient will lose the benefit of achieving SVR.
- All other model parameters remain unchanged.

b) Exploratory Analysis for Regimens Without Price Information

There were three drug regimens in which we were able to assess the efficacy and safety through the NMA in genotype 1, 3 and 4, but price information was not available as they have not yet been approved (Cost of Antiviral Therapy): (17) DAC24 + ASU24 (daclatasvir and asunaprevir for 24 weeks), (18) DAC24 + ASU24 + PR24 (daclatasvir, asunaprevir and PR for 24 weeks), and (19) DAC12 + SOF12 (daclatasvir and sofosbuvir for 12 weeks). These regimens were of interest for the cost effectiveness analysis because they were submitted as pre-NOC submissions to CDR at the time of analysis: daclatasvirdaclatasvirdaclatasvirdaclatasvir In this exploratory analysis, we assessed the cost-effectiveness of these regimens by assuming the price of these regimens ranged between $55,860 (cost of PAR/RIT12 + OMB12 + DAS12) to $67,000 (cost of SOF12 + LDV12).

Efficacy, adverse event and withdrawal inputs used for these exploratory analyses are presented in Appendix 2.

c) Exploratory Analysis for SOF8+LDV8 in Genotype 1 Naive Non-cirrhotic Patients

Health Canada has a special indication for treatment using (8) SOF8+LDV8. That is, the treatment should be used only for treatment naive patients with HCV RNA < 6 million. In this exploratory analysis, we assessed the cost-effectiveness of (8) SOF8+LDV8. Efficacy inputs used for this exploratory analysis are presented in Appendix 2. Adverse events and withdrawal rate were assumed to be the same as for (6) SOF12+LDV12.

d) Exploratory Analysis for PAR/RIT12 + OMB12 + DAS12 + RBV12 in Genotype 1 Cirrhotic Patients

For genotype 1 patients with cirrhosis, PAR/RIT12 + OMB12 + DAS12 + RBV12 could not be included in the base-case NMA for this population since the publication from the only available trial (TURQUOISE II[41]) grouped the baseline characteristics of the treatment naive and treatment-experienced patients together. As a result, a sensitivity analysis to bring this regimen into the NMA was performed in the Clinical Review by assuming that the combined baseline characteristics could be applied to the naïve and experienced subgroups. In this exploratory analysis, we assess the cost-effectiveness of PAR/RIT12 + OMB12 + DAS12 + RBV12 in genotype 1 treatment naive and experienced patients with cirrhosis based on the sensitivity analysis results presented in the Clinical Review report. Efficacy inputs used for this exploratory analysis are presented in Appendix 2.

e) Exploratory Analysis incorporating BOSON study results for Genotype 3 Patients

For genotype 3 patients, sensitivity analyses were performed to incorporate results from a recent RCT (BOSON Study)[42] presented at EASL 2015 into the NMA analyses, based on clinical expert input regarding the importance of this study. The BOSON trial compared So12 PR12 with SOF24 + RBV24 in patients with genotype 3 infection. In this exploratory analysis, we assessed the cost-effectiveness of (40) So12 PR12 in genotype 3 patients based on the sensitivity analysis results presented in the Clinical Review report. Efficacy inputs used for this exploratory analysis are presented in Appendix 2.

3.1.10 Sensitivity Analyses

a) One-Way Deterministic Sensitivity Analyses

Full deterministic one-way sensitivity analyses were performed on all model parameters to test the effect of changes in underlying parameter values and assumptions for treatment-naive and treatment-experienced patients.

The parameters that were varied in the deterministic sensitivity analyses, as well as the ranges considered, are presented in Table 15.

Table 15: Parameters Varied in the Deterministic Sensitivity Analyses	
Analyses	**Range/Alternate Source**
CHC infection-related Parameters	
CHC infection-related cost	± 25% reference value
CHC infection-related utilities	alternate source (Chong et al.)
CHC infection-related mortality	± 25% reference value
CHC infection progression rate (natural history)	± 95% CI limits
Treatment-Related Parameters	
Cost of antiviral therapy	± 25% reference value
Cost of adverse events	± 25% reference value
Disutility for adverse events	Assuming no additional disutility for anemia, depression and rash
Comparative efficacy (NMA results for SVR rates)	± 95% CrI limits
Comparative incidence of adverse events (NMA results for anemia, depression, rash)	± 95% CrI limits
Heterogeneity Parameters	
Fibrosis distribution	± 25% reference value
Baseline age	40 to 60 years
Discount rate	3% (instead of 5% in base case)

CHC = chronic hepatitis C; CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; RGT = response-guided therapy; SVR = sustained virologic response.

b) Probabilistic Sensitivity Analysis

For probabilistic sensitivity analysis (PSA), Monte Carlo simulations were used to explore all model strategies by running 2,000 iterations. All probabilistic parameters and utilities used in the model were represented by beta distributions formed by the corresponding ranges, as indicated in the previous subsection. All the cost parameters were represented by gamma distributions formed by the corresponding ranges, as indicated in Table 10 and Table 11. Treatment efficacy and adverse event parameters were represented by the prior distribution generated from the NMA (binomial distribution).

3.1.11 Model Validation

For validation purposes, the predictions of the current model, based on the baseline parameter values, were compared with external studies.[43-45] More specifically, outcomes compared included the probability of progression to cirrhosis and the probability of liver death (Table 16 and Table 17).

The current model's predictions closely matched those from a previous Canadian model developed by Krahn et al.[43] to assess the prognosis of hepatitis C patients infected by transfusion, with the probability of cirrhosis over 20 years (from the time of infection) being 15.0% and 13.9% in the current model the above cited model, respectively; the probability of liver-related death over 20 years (from the time of infection) is 2.6% and 2.5% in the current model and the above cited model, respectively.

Moreover, the results were also similar to a calibrated model by Salomon et al.,[44] using data from the US, where the probability of cirrhosis over 30 years (from the time of infection) was estimated at 35.5% and 30.0% in the current model and Salomon's model, respectively.

Table 16: Validation Results — Probability of Cirrhosis		
Studies	**20 Years**	**30 Years**
Current model (age 50 years)	15.0%	35.5%
Salomon et al. (age 40 years)[44]	Not reported	30.0%
Krahn et al. (mean age 67 years)[43]	13.9%	Not reported
Wong et al. (age 40 years)[45]	Not reported	41%

Table 17: Validation Results — Probability of Liver Death	
Studies	**20 Years**
Current model (age 50 years)	2.6%
Salomon et al. (age 40 years)[44]	Not reported
Krahn et al. (mean age 67 years)[43]	2.5%
Wong et al. (age 40 years)[45]	Not reported

4 PHARMCOECONOMIC RESULTS

4.1 Base-Case Analysis

4.1.1 Genotype 1: Treatment-Naive: Non-cirrhotic

Table 18 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 1, treatment-naive non-cirrhotic patients, when the baseline fibrosis distribution is applied.

The interferon-free drugs are more costly but more effective than PR. Among the interferon-free drugs, (14) PAR/RIT12 + OMB12 + DAS12 was the most cost-effective treatment (ICUR of $29,354 per QALY), when compared with PR therapy.

(14) PAR/RIT12 + OMB12 + DAS12 was associated with an increase in health (0.996 QALY) and cost ($29,247), resulting in an ICUR of $29,354 per QALY compared with PR therapy. (6) SOF12 + LDV12 was the most effective treatment in terms of total QALY (11.857 QALY) generated, it was associated with an increase in health (1.018 QALY) and cost ($38,631), resulting in an ICUR of $37,951 per QALY compared with PR therapy.

Table 18: Results of Base-Case Deterministic Analysis (Genotype 1 Treatment-Naive Non-cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(0) no treatment	$104,904	9.734	-	-	-	-
(1) PR48	$114,132	10.839	-	-	-	$8,353
(14) PAR/RIT12 + OMB12 + DAS12	$143,379	11.835	$29,247	0.996	$29,354	$29,354
(6) SOF12 + LDV12	$152,762	11.857	$38,631	1.018	$37,951	$435,528
Dominated or Extendedly Dominated[a] Treatments						
(46) B24 PR28-48 RGT	$135,218	11.370	$21,086	0.531	$39,710	ext. dominated
(42) Si12 PR24-48	$136,770	11.449	$22,638	0.610	$37,106	ext.

Table 18: Results of Base-Case Deterministic Analysis (Genotype 1 Treatment-Naive Non-cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
RGT						dominated
(32) T12 PR24-48 RGT q8	$137,381	11.400	$23,250	0.561	$41,452	dominated
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$146,021	11.841	$31,890	1.002	$31,823	ext. dominated
(40) So12 PR12	$146,140	11.651	$32,008	0.812	$39,431	dominated
(41) So12 PR24-48 RGT	$150,969	11.589	$36,837	0.750	$49,113	dominated
(5) SIM12 + SOF12	$178,356	11.700	$64,224	0.861	$74,582	dominated
(72) SOF12+ SIM12+RBV12	$182,383	11.655	$68,251	0.816	$83,618	dominated
(4) SOF24 + RBV24	$201,979	11.497	$87,847	0.658	$133,509	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description; QALY = quality-adjusted life-year.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.1.2 Genotype 1: Treatment-Naive: Non-cirrhotic: By Fibrosis Stage

Without placing implicit fibrosis distribution assumptions on the treatment population, Table 19 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 1, treatment-naive non-cirrhotic patients with PR as a reference by fibrosis stages.

Across all fibrosis stages, (14) PAR/RIT12 + OMB12 + DAS12 was the most cost-effective treatment option compared with PR.

Table 19: Results of Base-Case Deterministic Analysis (Genotype 1 Treatment-Naive Non-cirrhotic Patients) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
F0						
(0) no treatment	$106,540	10.699	-	-	-	-
(1) PR48	$114,884	11.277	-	-	-	$14,444
(14) PAR/RIT12 + OMB12 + DAS12	$143,450	11.884	$28,566	0.607	$47,066	$47,066
(6) SOF12 + LDV12	$152,821	11.897	$37,937	0.620	$61,151	$696,970
Dominated or Extendedly Dominated[a] Treatments						
(46) B24 PR28-48 RGT	$130,368	11.590	$15,484	0.313	$49,546	ext. dominated
(42) Si12 PR24-48 RGT	$137,095	11.643	$22,211	0.366	$60,659	ext. dominated
(32) T12 PR24-48 RGT q8	$137,728	11.608	$22,845	0.331	$69,067	dominated

Table 19: Results of Base-Case Deterministic Analysis (Genotype 1 Treatment-Naive Non-cirrhotic Patients) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$146,083	11.884	$31,199	0.607	$51,370	ext. dominated
(40) So12 PR12	$146,334	11.770	$31,450	0.493	$63,810	dominated
(41) So12 PR24-48 RGT	$151,193	11.725	$36,309	0.448	$80,964	dominated
(5) SIM12 + SOF12	$178,525	11.805	$63,641	0.528	$120,643	dominated
(72) SOF12+ SIM12+RBV12	$182,579	11.774	$67,695	0.497	$136,085	dominated
(4) SOF24 + RBV24	$202,271	11.672	$87,387	0.395	$221,062	dominated
F1						
(0) no treatment	$106,094	10.428	-	-	-	-
(1) PR48	$114,691	11.156	-	-	-	$11,809
(14) PAR/RIT12 + OMB12 + DAS12	$143,429	11.871	$28,738	0.715	$40,192	$40,192
(6) SOF12 + LDV12	$152,803	11.886	$38,111	0.730	$52,194	$618,316
Dominated or Extendedly Dominated[a] Treatments						
(46) B24 PR28-48 RGT	$130,272	11.530	$15,580	0.374	$41,701	ext. dominated
(42) Si12 PR24-48 RGT	$137,009	11.590	$22,318	0.433	$51,491	ext. dominated
(32) T12 PR24-48 RGT q8	$137,637	11.550	$22,945	0.394	$58,195	dominated
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$146,065	11.873	$31,373	0.717	$43,761	ext. dominated
(40) So12 PR12	$146,281	11.737	$31,589	0.581	$54,390	dominated
(41) So12 PR24-48 RGT	$151,133	11.688	$36,442	0.532	$68,484	dominated
(5) SIM12 + SOF12	$178,478	11.776	$63,786	0.620	$102,963	dominated
(72) SOF12+ SIM12+RBV12	$182,525	11.741	$67,834	0.585	$115,957	dominated
(4) SOF24 + RBV24	$202,193	11.624	$87,502	0.468	$187,071	dominated
F2						
(0) no treatment	$104,837	9.724	-	-	-	-
(1) PR48	$114,110	10.837	-	-	-	$8,331
(14) PAR/RIT12 + OMB12 + DAS12	$143,369	11.838	$29,259	1.001	$29,242	$29,242
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$146,011	11.843	$31,901	1.006	$31,700	$456,822
(6) SOF12 + LDV12	$152,750	11.857	$38,641	1.020	$37,875	$485,936
Dominated or Extendedly Dominated[a] Treatments						
(46) B24 PR28-48 RGT	$130,037	11.373	$15,927	0.535	$29,746	ext. dominated

Table 19: Results of Base-Case Deterministic Analysis (Genotype 1 Treatment-Naive Non-cirrhotic Patients) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(42) Si12 PR24-48 RGT	$136,753	11.449	$22,644	0.611	$37,030	ext. dominated
(32) T12 PR24-48 RGT q8	$137,362	11.399	$23,252	0.562	$41,346	dominated
(40) So12 PR12	$146,124	11.651	$32,015	0.813	$39,355	dominated
(41) So12 PR24-48 RGT	$150,956	11.590	$36,846	0.753	$48,909	dominated
(5) SIM12 + SOF12	$178,341	11.700	$64,231	0.863	$74,436	dominated
(72) SOF12+ SIM12+RBV12	$182,367	11.654	$68,258	0.817	$83,574	dominated
(4) SOF24 + RBV24	$201,962	11.497	$87,853	0.659	$133,213	dominated
F3						
(0) no treatment	$103,259	8.723	-	-	-	-
(1) PR48	$113,349	10.373	-	-	-	$6,113
(14) PAR/RIT12 + OMB12 + DAS12	$143,322	11.779	$29,973	1.406	$21,322	$21,322
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,973	11.790	$32,625	1.417	$23,023	$234,552
(6) SOF12 + LDV12	$152,722	11.813	$39,373	1.440	$27,350	$299,154
Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$136,446	11.242	$23,097	0.869	$26,581	ext. dominated
(32) T12 PR24-48 RGT q8	$137,039	11.178	$23,690	0.805	$29,439	dominated
(40) So12 PR12	$145,957	11.523	$32,608	1.150	$28,348	dominated
(46) B24 PR28-48 RGT	$150,412	11.130	$37,063	0.757	$48,979	dominated
(41) So12 PR24-48 RGT	$150,750	11.440	$37,401	1.067	$35,052	dominated
(5) SIM12 + SOF12	$178,200	11.588	$64,851	1.215	$53,361	dominated
(72) SOF12+ SIM12+RBV12	$182,198	11.530	$68,850	1.157	$59,504	dominated
(4) SOF24 + RBV24	$201,690	11.310	$88,341	0.937	$94,308	dominated

ext = extendedly; F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; ICUR=incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.1.3 Genotype 1: Treatment-Naive: Cirrhotic

Table 20 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 1, treatment-naive patients with cirrhosis.

The interferon-free drugs are more costly but more effective than PR. Among the interferon-free drugs, (6) SOF12 + LDV12 was the most cost-effective treatment (ICUR of $26,261 per QALY)

when compared with PR therapy. (6) SOF12 + LDV12 was associated with an increase in health (1.879 QALY) and cost ($49,344), resulting in an ICUR of $26,261 per QALY compared with PR therapy.

Other treatment options were ruled out either because they were absolutely dominated or extendedly dominated by the other treatments.

Table 20: Results of Base-Case Deterministic Analysis (Genotype 1 Treatment-Naive Cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference

Treatment	Total Cost	Total QALYs	Versus PR Alone			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$120,140	8.659	-	-	-	$11,628
(6) SOF12 + LDV12	$169,483	10.538	$49,344	1.879	$26,261	$26,261
Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$149,012	9.557	$28,872	0.899	$32,123	ext. dominated
(32) T12 PR24-48 RGT q8	$153,580	9.219	$33,441	0.561	$59,622	dominated
(46) B24 PR28-48 RGT	$160,651	8.189	$40,512	0–.470	dominated	dominated
(40) So12 PR12	$160,816	10.009	$40,676	1.351	$30,115	ext. dominated
(5) SIM12 + SOF12	$193,471	10.212	$73,332	1.553	$47,208	dominated
(4) SOF24 + RBV24	$214,699	9.636	$94,559	0.978	$96,723	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.1.4 Genotype 1: Treatment-Experienced Patients: Non-cirrhotic

Table 21 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 1 treatment-experienced non-cirrhotic patients.

The interferon-free drugs are more costly but more effective than PR. Among the interferon-free drugs, (14) PAR/RIT12 + OMB12 + DAS12 was the most cost-effective treatment (ICUR of $15,506 per QALY) when compared with PR therapy. (14) PAR/RIT12 + OMB12 + DAS12 was associated with an increase in health (1.586QALY) and cost ($24,597), resulting in an ICUR of $15,506 per QALY compared with PR therapy.

(15) PAR/RIT12 + OMB12 + DAS12 + RBV12 was the most effective treatment in terms of total QALY (11.898 QALY), it was associated with an increase in health (1.616 QALY) and cost ($27,422), resulting in an ICUR of $16,965 per QALY compared with PR therapy. Other treatment options were ruled out either because they were absolutely dominated or extendedly dominated by the other treatments.

Table 21: Results of Base-Case Deterministic Analysis (Genotype 1: Treatment-Experienced Non-cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(0) no treatment	$104,668	9.596	-	-	-	-
(1) PR48	$118,321	10.282	-	-	-	**ext. dominated**
(14) PAR/RIT12 + OMB12 + DAS12	$142,917	11.868	$24,597	1.586	$15,506	$16,836
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,743	11.898	$27,422	1.616	$16,965	$93,872
Other Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$138,660	11.169	$20,339	0.887	$22,918	ext. dominated
(39) T12 PR48 q8	$142,464	11.394	$24,143	1.113	$21,702	ext. dominated
(74) B32 PR36-48 RGT	$143,264	11.122	$24,943	0.841	$29,675	dominated
(68) Si12 PR48	$143,840	11.406	$25,519	1.124	$22,702	dominated
(40) So12 PR12	$150,153	11.471	$31,833	1.189	$26,770	dominated
(6) SOF12 + LDV12	$154,321	11.761	$36,001	1.480	$24,329	dominated
(72) SOF12+ SIM12+RBV12	$186,875	11.046	$68,554	0.765	$89,659	dominated
(5) SIM12 + SOF12	$189,079	10.280	$70,758	0–.001	abs. dominated	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.1.5 Genotype 1: Treatment-Experienced Patients: Non-cirrhotic: By Fibrosis Stage

Table 22 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 1, treatment-experienced non-cirrhotic patients using PR as a reference by fibrosis stages.

Across all fibrosis stages, (14) PAR/RIT12 + OMB12 + DAS12 was the most cost-effective treatment option, followed by (15) PAR/RIT12 + OMB12 + DAS12 + RBV12, compared with PR.

Table 22: Results of Base-Case Deterministic Analysis (Genotype 1: Treatment-Experienced Patients: Non-cirrhotic) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
F0						
(0) no treatment	$106,540	10.699	-	-	-	-
(1) PR48	$119,576	11.007	-	-	-	ext. dominated
(14) PAR/RIT12 + OMB12 + DAS12	$142,970	11.907	$23,394	0.901	$25,976	$30,154
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,766	11.920	$26,190	0.913	$28,671	$217,266
Other Dominated Or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$139,235	11.508	$19,659	0.501	$39,229	ext. dominated
(39) T12 PR48 q8	$142,829	11.611	$23,253	0.604	$38,493	ext. dominated
(74) B32 PR36-48 RGT	$143,275	11.465	$23,698	0.458	$51,739	dominated
(68) Si12 PR48	$144,201	11.620	$24,625	0.613	$40,152	dominated
(40) So12 PR12	$150,507	11.683	$30,931	0.676	$45,742	dominated
(6) SOF12 + LDV12	$154,459	11.849	$34,883	0.842	$41,409	dominated
(72) SOF12+ SIM12+RBV12	$187,569	11.454	$67,993	0.447	$152,204	dominated
(5) SIM12 + SOF12	$190,385	11.042	$70,809	0.035	$2,028,564	dominated
F1						
(0) no treatment	$106,094	10.428	-	-	-	-
(1) PR48	$119,299	10.832	-	-	-	ext. dominated
(14) PAR/RIT12 + OMB12 + DAS12	$142,956	11.899	$23,657	1.067	$22,180	$25,067
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,758	11.916	$26,460	1.084	$24,416	$164,114
Other Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$139,104	11.426	$19,805	0.594	$33,343	ext. dominated
(39) T12 PR48 q8	$142,747	11.559	$23,448	0.727	$32,258	ext. dominated
(74) B32 PR36-48 RGT	$143,143	11.382	$23,844	0.550	$43,321	dominated
(68) Si12 PR48	$144,120	11.569	$24,821	0.737	$33,690	dominated
(40) So12 PR12	$150,424	11.632	$31,125	0.800	$38,920	dominated
(6) SOF12 +	$154,425	11.828	$35,127	0.996	$35,261	dominated

Table 22: Results of Base-Case Deterministic Analysis (Genotype 1: Treatment-Experienced Patients: Non-cirrhotic) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
LDV12						
(72) SOF12+ SIM12+RBV12	$187,408	11.354	$68,110	0.522	$130,442	dominated
(5) SIM12 + SOF12	$190,084	10.856	$70,786	0.024	$2,932,294	dominated
F2						
(0) no treatment	$104,837	9.724	-	-	-	-
(1) PR48	$118,455	10.370	-	-	-	ext. dominated
(14) PAR/RIT12 + OMB12 + DAS12	$142,914	11.875	$24,459	1.506	$16,246	$17,698
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,737	11.904	$27,282	1.534	$17,789	$100,425
Other Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$138,712	11.210	$20,257	0.840	$24,103	ext. dominated
(39) T12 PR48 q8	$142,496	11.422	$24,041	1.052	$22,861	ext. dominated
(74) B32 PR36-48 RGT	$142,751	11.165	$24,297	0.795	$30,563	dominated
(68) Si12 PR48	$143,872	11.433	$25,417	1.063	$23,909	dominated
(40) So12 PR12	$150,180	11.497	$31,726	1.127	$28,141	dominated
(6) SOF12 + LDV12	$154,325	11.773	$35,871	1.403	$25,566	dominated
(72) SOF12+ SIM12+RBV12	$186,937	11.094	$68,482	0.724	$94,624	dominated
(5) SIM12 + SOF12	$189,204	10.370	$70,750	0.000	abs. dominated	dominated
F3						
(0) no treatment	$103,259	8.723	-	-	-	-
(1) PR48	$117,329	9.699	-	-	-	ext. dominated
(14) PAR/RIT12 + OMB12 + DAS12	$142,892	11.831	$25,564	2.133	$11,987	$12,749
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,741	11.875	$28,413	2.176	$13,055	$65,111
Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$138,222	10.897	$20,893	1.198	$17,437	ext. dominated
(39) T12 PR48 q8	$142,189	11.218	$24,860	1.520	$16,361	ext. dominated
(68) Si12 PR48	$143,568	11.232	$26,239	1.533	$17,119	dominated

Table 22: Results of Base-Case Deterministic Analysis (Genotype 1: Treatment-Experienced Patients: Non-cirrhotic) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(74) B32 PR36-48 RGT	$144,178	10.845	$26,850	1.146	$23,422	dominated
(40) So12 PR12	$149,895	11.299	$32,566	1.600	$20,348	dominated
(6) SOF12 + LDV12	$154,232	11.689	$36,904	1.991	$18,540	dominated
(72) SOF12+ SIM12+RBV12	$186,351	10.723	$69,022	1.025	$67,371	dominated
(5) SIM12 + SOF12	$188,075	9.675	$70,747	0–.024	abs. dominated	dominated

ext = extendedly; F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis**;** ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.1.6 Genotype 1: Treatment-Experienced Patients: Cirrhotic

Table 23 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 1, treatment-experienced patients with cirrhosis. At the baseline estimate, the PR-based DAAs and interferon-free drugs are more costly but more effective than PR alone.

Among the PR-based DAA and interferon-free drugs, (42) Si12 PR24-48 RGT was the most cost-effective treatment (ICUR of $20,655 per QALY), followed by (10) SOF12 + LDV12 + RBV12 (ICUR of $26,456 per QALY) when compared with PR therapy.

(42) Si12 PR24-48 RGT was associated with an increase in health (1.402 QALY) and cost ($28,953), resulting in an ICUR of $20,655 per QALY compared with PR therapy. (10) SOF12 + LDV12 + RBV12 was associated with an increase in health (2.009 QALY) and cost ($53,148), resulting in an ICUR of $26,456 per QALY compared with PR therapy. (5) SIM12 + SOF12 was the most effective treatment in terms of total QALY (9.966 QALY) generated, it was associated with an increase in health (2.041 QALY) and cost ($73,225), resulting in an ICUR of $35,870 per QALY compared with PR therapy.

Table 23: Results of Base-Case Deterministic Analysis (Genotype 1: Treatment-Experienced Cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$119,828	7.924	-	-	-	ext. dominated[a]
(42) Si12 PR24-48 RGT	$148,780	9.326	$28,953	1.402	$20,655	$20,774
(10) SOF12 + LDV12 + RBV12	$172,976	9.933	$53,148	2.009	$26,456	$39,845
(5) SIM12 + SOF12	$193,052	9.966	$73,225	2.041	$35,870	$618,881
Dominated or Extendedly Dominated Treatments						
(74) B32 PR36-48 RGT	$153,492	8.758	$33,664	0.834	$40,357	dominated
(39) T12 PR48 q8	$153,691	9.046	$33,863	1.122	$30,190	dominated
(68) Si12 PR48	$154,912	8.879	$35,084	0.954	$36,757	dominated
(40) So12 PR12	$162,499	8.941	$42,671	1.017	$41,954	dominated
(7) SOF24 + LDV24	$234,378	9.887	$114,550	1.962	$58,371	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year.
Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.1.7 Genotype 2: Treatment-Naive: Non-cirrhotic

Table 24 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 2, treatment-naive non-cirrhotic patients, when the baseline fibrosis distribution is applied.

The PR-based DAA and the interferon-free drug are more costly but more effective than PR. (40) So12 PR12 was the most expensive treatment ($145,731), followed by (3) SOF12 + RBV12 ($143,955), then (70) PR24 ($99,904).

(3) SOF12 + RBV12 was associated with an increase in health (0.217 QALY) and cost ($44,051), resulting in an ICUR of $203,282 per QALY compared with PR therapy. (40) So12 PR12 was dominated by (3) SOF12 + RBV12 (as (40) So12 PR12 was more expensive, but resulted in less QALY gains than (3) SOF12 + RBV12).

Table 24: Results of Base-Case Deterministic Analysis (Genotype 2: Treatment-Naive Non-cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(70) PR24	$99,904	11.532	-	-	-	-
(3) SOF12 + RBV12	$143,955	11.749	$44,051	0.217	$203,282	$203,282
Dominated treatments						
(0) no treatment	$104,904	9.734	$5,000	1–.798	dominated	dominated
(40) So12 PR12	$145,731	11.698	$45,827	0.166	$276,103	dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.

4.1.8 Genotype 2: Treatment-Naive: Non-cirrhotic: By Fibrosis Stage

Without placing implicit fibrosis distribution assumptions on the treatment population, Table 25 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 2, treatment-naive non-cirrhotic patients with PR as a reference by fibrosis stages.

Across all fibrosis stages, no PR-based DAA or interferon-free regimen was cost-effective (all ICURs > $100,000), when compared with PR.

Table 25: Results of Base-Case Deterministic Analysis (Genotype 2: Treatment-Naive Non-cirrhotic Patients) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
F0						
(70) PR24	100171.8	11.693	-	-	-	-
(3) SOF12 + RBV12	144083.3	11.830	$43,911	0.137	$320,829	$320,829
Dominated Treatments						
(0) no treatment	106540	10.699	$6,368	–0.994	dominated	dominated
(40) So12 PR12	145890.8	11.798	$45,719	0.105	$435,246	dominated
F1						
(70) PR24	100100.3	11.649	-	-	-	-
(3) SOF12 + RBV12	144047	11.807	$43,947	0.159	$276,590	$276,590
Dominated Treatments						
(0) no treatment	106093.7	10.428	$5,993	–1.221	dominated	dominated
(40) So12 PR12	145846.7	11.771	$45,746	0.122	$374,127	dominated
F2						
(70) PR24	99888.23	11.532	-	-	-	-
(3) SOF12 + RBV12	143940.7	11.749	$44,052	0.217	$203,052	$203,052
Dominated Treatments						
(0) no treatment	104836.7	9.724	$4,948	–1.808	dominated	dominated
(40) So12 PR12	145717.8	11.700	$45,830	0.168	$273,119	dominated
F3						
(70) PR24	99640.9	11.360	-	-	-	-
(3) SOF12 + RBV12	143840.3	11.661	$44,199	0.302	$146,489	$146,489

Table 25: Results of Base-Case Deterministic Analysis (Genotype 2: Treatment-Naive Non-cirrhotic Patients) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Dominated Treatments						
(0) no treatment	103259.4	8.723	$3,618	–2.637	dominated	dominated
(40) So12 PR12	145580.2	11.587	$45,939	0.228	$201,698	dominated

F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; ICUR=incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.9 Genotype 2: Treatment-Naive: Cirrhotic

Table 26 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 2, treatment-naive patients with cirrhosis. (3) SOF12 + RBV12 are more costly but more effective than PR. (3) SOF12 + RBV12 was associated with an increase in health (0.797 QALY) and cost ($46,773), resulting in an ICUR of $58,659 per QALY compared with PR therapy.

Table 26: Results of Base-Case Deterministic Analysis (Genotype 2: Treatment-Naive cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(0) no treatment	$101,355	7.043	-	-	-	-
(70) PR24	$112,767	9.384	-	-	-	$4,876
(3) SOF12 + RBV12	$159,541	10.181	$46,773	0.797	$58,659	$58,659

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin.

4.1.10 Genotype 2: Treatment-Experienced Patients: Non-cirrhotic

Table 27 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 2, treatment-experienced non-cirrhotic patients, when the baseline fibrosis distribution is applied. The PR-based DAA and the interferon-free regimens are more costly but more effective than no treatment. (40) So12 PR12 was the most expensive treatment ($145,460), followed by (3) SOF12 + RBV12 ($144,023).

(3) SOF12 + RBV12 was associated with an increase in health (2.157 QALY) and cost ($39,355), resulting in an ICUR of $18,247 per QALY compared with **no treatment**. (40) So12 PR12 was dominated by (3) SOF12 + RBV12 (as (40) So12 PR12 was more expensive, but resulted in less QALY gains than (3) SOF12 + RBV12).

Table 27: Results of Base-Case Deterministic Analysis (Genotype 2: Treatment-Experienced Non-cirrhotic Patients) With No Treatment as Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(0) no treatment	$104,668	9.596	-	-	-	-
(3) SOF12 + RBV12	$144,023	11.753	$39,355	2.157	$18,247	$18,247
Dominated Treatments						
(40) So12 PR12	$145,460	11.689	$40,791	2.092	$19,494	dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.11 Genotype 2: Treatment-Experienced Patients: Non-cirrhotic: By Fibrosis Stage

Table 28 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 2, treatment-experienced non-cirrhotic patients using **no treatment** as a reference by fibrosis stages.

Across all fibrosis stages, (3) SOF12 + RBV12 was the most cost-effective treatment option compared with **no treatment**. (40) So12 PR12 was dominated by (3) SOF12 + RBV12 (as (40) So12 PR12 was more expensive, but resulted in less QALY gains than (3) SOF12 + RBV12).

Table 28: Results of Base-Case Deterministic Analysis (Genotype 2: Treatment-Experienced Non-cirrhotic Patients) With No Treatment as Reference by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
F0						
(0) no treatment	$106,540	10.699	-	-	-	-
(3) SOF12 + RBV12	$144,156	11.838	$37,616	1.139	$33,037	$33,037
Dominated Treatments						
(40) So12 PR12	$145,641	11.801	$39,101	1.102	$35,491	dominated
F1						
(0) no treatment	$106,094	10.428	-	-	-	-
(3) SOF12 + RBV12	$144,123	11.818	$38,029	1.389	$27,370	$27,370
Dominated Treatments						
(40) So12 PR12	$145,597	11.774	$39,503	1.346	$29,354	dominated
F2						
(0) no treatment	$104,837	9.724	-	-	-	-
(3) SOF12 + RBV12	$144,026	11.764	$39,190	2.040	$19,209	$19,209
Dominated Treatments						
(40) So12 PR12	$145,468	11.703	$40,631	1.979	$20,535	dominated
F3						
(0) no treatment	$103,259	8.723	-	-	-	-
(3) SOF12 + RBV12	$143,938	11.683	$40,678	2.960	$13,741	$13,741
Dominated Treatments						
(40) So12 PR12	$145,338	11.598	$42,078	2.875	$14,636	dominated

F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; ICUR=incremental cost-utility ratio; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.12 Genotype 2: Treatment-Experienced: Cirrhotic

Table 29 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 2, treatment-experienced patients with cirrhosis. (73) SOF16 + RBV16 was the most expensive treatment ($177,502), followed by (40) So12 PR12 ($160,863), then (3) SOF12 + RBV12 ($159,347).

(40) So12 PR12 was associated with an increase in health (3.265 QALY) and cost ($59,508), resulting in an ICUR of $18,226 per QALY compared with **no treatment**. (3) SOF12 + RBV12 was extendedly dominated by no treatment and (40) So12 PR12. (73) SOF16 + RBV16 was dominated by (40) So12 PR12 (as (73) SOF16 + RBV16 was more expensive, but resulted in less QALY gains than (40) So12 PR12).

Table 29: Results of Base-Case Deterministic Analysis (Genotype 2: Treatment-Experienced Cirrhotic Patients) With No Treatment as a Reference

Treatment	Total Cost	Total QALYs	Versus No Treatment			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
(0) no treatment	$101,355	7.043	-	-	-	-
(40) So12 PR12	$160,863	10.308	$59,508	3.265	$18,226	$18,226
Dominated or Extendedly Dominated[a] Treatments						
(3) SOF12 + RBV12	$159,347	9.761	$57,992	2.718	$21,338	ext. dominated
(73) SOF16 + RBV16	$177,502	9.896	$76,147	2.853	$26,694	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.1.13 Genotype 3: Treatment-Naive: Non-cirrhotic

Table 30 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 3, treatment-naive non-cirrhotic patients, when the baseline fibrosis distribution is applied.

The interferon-free regimen is more costly but more effective than PR. (4) SOF24 + RBV24 was associated with an increase in health (0.578 QALY) and cost ($89,351), resulting in an ICUR of $154,599 per QALY compared with PR therapy.

Table 30: Results of Base-Case Deterministic Analysis (Genotype 3: Treatment-Naive Non-cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference

Treatment	Total Cost	Total QALYs	Versus PR Alone			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
(0) no treatment	$104,184	9.314	-	-	-	-
(1) PR48	$110,387	11.156	-	-	-	$3,367
(4) SOF24 + RBV24	$199,738	11.734	$89,351	0.578	$154,599	$154,599

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.

4.1.14 Genotype 3: Treatment-Naive: Non-cirrhotic: By Fibrosis Stage

Without placing implicit fibrosis distribution assumptions on the treatment population, Table 31 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 3, treatment-naive non-cirrhotic patients with PR as a reference by fibrosis stages.

Across all fibrosis stages, (4) SOF24 + RBV24 was not cost-effective (all ICURs > $100,000), when compared with PR.

Table 31: Results of Base-Case Deterministic Analysis (Genotype 3: Treatment-Naive Non-cirrhotic Patients) by Fibrosis Stages

Fibrosis Stage, Treatment	Total Cost	Total QALYs	Versus PR Alone			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
F0						
(0) no treatment	$106,085	10.397	-	-	-	-
(1) PR48	$110,907	11.447	-	-	-	$4,590
(4) SOF24 + RBV24	$199,852	11.806	$88,945	0.359	$247,949	$247,949
F1						
(0) no treatment	$105,375	10.025	-	-	-	-
(1) PR48	$110,716	11.349	-	-	-	$4,036
(4) SOF24 + RBV24	$199,806	11.782	$89,089	0.433	$205,679	$205,679
F2						
(0) no treatment	$103,968	9.243	-	-	-	-
(1) PR48	$110,321	11.139	-	-	-	$3,351
(4) SOF24 + RBV24	$199,710	11.731	$89,389	0.592	$151,071	$151,071
F3						
(0) no treatment	$102,684	8.343	-	-	-	-
(1) PR48	$109,983	10.891	-	-	-	$2,865
(4) SOF24 + RBV24	$199,675	11.667	$89,693	0.776	$115,513	$115,513

F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; ICUR=incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.15 Genotype 3: Treatment-Naive: Cirrhotic

Table 32 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 3, treatment-naive patients with cirrhosis. The interferon-free regimen is more costly but more effective than PR. (4) SOF24 + RBV24 was associated with an increase in health (1.027 QALY) and cost ($94,594), resulting in an ICUR of $92,117 per QALY compared with PR therapy.

Table 32: Results of Base-Case Deterministic Analysis (Genotype 3: Treatment-Naive Cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference						
Treatment	Total Cost	Total QALYs	Versus PR Alone			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$120,843	9.335	-	-	-	$8,504
(4) SOF24 + RBV24	$215,437	10.362	$94,594	1.027	$92,117	$92,117

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.

4.1.16 Genotype 3: Treatment-Experienced Patients: Non-cirrhotic

Table 33 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 3, treatment-experienced non-cirrhotic patients, when the baseline fibrosis distribution is applied. The PR-based DAA and the interferon-free drug are more costly but more effective than no treatment. (4) SOF24 + RBV24 was the most expensive treatment ($200,324), followed by (40) So12 PR12 ($149,249).

(40) So12 PR12 was associated with an increase in health (2.343 QALY) and cost ($45,316), resulting in an ICUR of $19,339 per QALY compared with **no treatment**. (4) SOF24 + RBV24 was the most effective treatment in terms of total QALY (11.637 QALY) generated, and was associated with an increase in health (2.470 QALY) and cost ($96,392), resulting in an ICUR of $39,025 per QALY compared with **no treatment**.

Table 33: Results of Base-Case Deterministic Analysis (Genotype 3: Treatment-Experienced Non-cirrhotic Patients) With No Treatment as Reference					
Treatment	Total Cost	Total QALYs	Versus No Treatment		
			Incremental Cost	Incremental QALYs	ICUR
(0) no treatment	$103,932	9.167	-	-	-
(1) PR48	$112,301	10.879	$8,368	1.712	$4,888
(40) So12 PR12	$149,249	11.510	$45,316	2.343	$19,339
(4) SOF24 + RBV24	$200,324	11.637	$96,392	2.470	$39,025

ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.17 Genotype 3: Treatment-Experienced Patients: Non-cirrhotic: By Fibrosis Stage

Table 34 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 3, treatment-experienced non-cirrhotic patients using **no treatment** as a reference by fibrosis stages.

Across all fibrosis stages, (40) So12 PR12 was the most cost-effective treatment option compared with **no treatment**, followed by (4) SOF24 + RBV24 compared with **no treatment.**

Table 34: Results of Base-Case Deterministic Analysis (Genotype 3: Treatment-Experienced Non-cirrhotic Patients) by Fibrosis Stages					
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**		
			Incremental Cost	**Incremental QALYs**	**ICUR**
F0					
(0) no treatment	$106,085	10.397			
(1) PR48	$113,084	11.313	$6,999	0.916	$7,639
(40) So12 PR12	$149,563	11.695	$43,478	1.298	$33,490
(4) SOF24 + RBV24	$200,531	11.761	$94,446	1.365	$69,205
F1					
(0) no treatment	$105,374	10.025			
(1) PR48	$112,833	11.184	$7,459	1.159	$6,438
(40) So12 PR12	$149,457	11.640	$44,082	1.615	$27,300
(4) SOF24 + RBV24	$200,460	11.725	$95,085	1.700	$55,946
F2					
(0) no treatment	$103,968	9.243			
(1) PR48	$112,312	10.908	$8,344	1.665	$5,010
(40) So12 PR12	$149,241	11.523	$45,273	2.280	$19,856
(4) SOF24 + RBV24	$200,314	11.647	$96,346	2.404	$40,082
F3					
(0) no treatment	$102,684	8.343			
(1) PR48	$111,844	10.583	$9,160	2.240	$4,089
(40) So12 PR12	$149,090	11.384	$46,406	3.041	$15,259
(4) SOF24 + RBV24	$200,228	11.550	$97,544	3.207	$30,413

F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; ICUR=incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.18 Genotype 3: Treatment-Experienced: Cirrhotic

Table 35 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 3, treatment-experienced patients with cirrhosis. (4) SOF24 + RBV24 was the most expensive treatment ($214,706), followed by (40) So12 PR12 ($163,647).

(40) So12 PR12 was associated with an increase in health (3.039 QALY) and cost ($62,292), resulting in an ICUR of $20,496 per QALY compared with **no treatment**. (4) SOF24 + RBV24 was dominated by (40) So12 PR12 (as (4) SOF24 + RBV24 was more expensive, but resulted in less QALY gains than (40) So12 PR12).

Table 35: Results of Base-Case Deterministic Analysis (Genotype 3: Treatment-Experienced Cirrhotic Patients) With No Treatment as a Reference					
Treatment	Total Cost	Total QALYs	Versus No Treatment		
			Incremental Cost	Incremental QALYs	ICUR
(0) no treatment	$101,355	7.043			
(1) PR48	$120,880	8.936	$19,525	1.893	$10,317
(40) So12 PR12	$163,647	10.082	$62,292	3.039	$20,496
(4) SOF24 + RBV24	$214,706	9.661	$113,351	2.618	$43,292

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.

4.1.19 Genotype 4: Treatment-Naive: Non-cirrhotic

Table 36 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 4, treatment-naive non-cirrhotic patients, when the baseline fibrosis distribution is applied. It should be noted that So12 PR12, which is indicated for treatment of genotype 4 infection, could not be included in the cost effectiveness analysis as there were insufficient subgroup data by cirrhosis status to include this regimen in the cirrhosis and non-cirrhosis NMAs in the Clinical Review.

The interferon-free regimens (4) SOF24 + RBV24 was associated with an increase in health (0.395 QALY) and cost ($90,021), resulting in an ICUR of $227,716 per QALY compared with PR therapy.

Table 36: Results of Base-Case Deterministic Analysis (Genotype 4: Treatment-Naive Non-cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference						
Treatment	Total Cost	Total QALYs	Versus PR Alone			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
(0) no treatment	$104,904	9.734	-	-	-	-
(1) PR48	$111,496	11.158	-	-	-	$4,631
(4) SOF24 + RBV24	$201,517	11.553	$90,021	0.395	$227,716	$227,901

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.

4.1.20 Genotype 4: Treatment-Naive: Non-cirrhotic: By Fibrosis Stage

Without placing implicit fibrosis distribution assumptions on the treatment population, Table 37 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 4, treatment-naive non-cirrhotic patients with PR as a reference by fibrosis stages.

Across all fibrosis stages, (4) SOF24 + RBV24 was not cost-effective (all ICURs > $100,000), when compared with PR.

Table 37: Results of Base-Case Deterministic Analysis (Genotype 4: Treatment-Naive Non-cirrhotic Patients) by Fibrosis Stages						
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
F0						
(0) no treatment	$106,540	10.699	-	-	-	-
(1) PR48	$112,014	11.462	-	-	-	$7,180
(4) SOF24 + RBV24	$201,768	11.705	$89,754	0.243	$369,661	$369,661
F1						
(0) no treatment	$106,094	10.428	-	-	-	-
(1) PR48	$111,880	11.378	-	-	-	$6,092
(4) SOF24 + RBV24	$201,701	11.663	$89,821	0.285	$315,469	$315,469
F2						
(0) no treatment	$104,837	9.724	-	-	-	-
(1) PR48	$111,477	11.157	-	-	-	$4,635
(4) SOF24 + RBV24	$201,501	11.552	$90,023	0.396	$227,554	$227,554
F3						
(0) no treatment	$103,259	8.723	-	-	-	-
(1) PR48	$110,964	10.833	-	-	-	$3,650
(4) SOF24 + RBV24	$201,272	11.392	$90,308	0.558	$161,766	$161,766

F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; ICUR=incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.21 Genotype 4: Treatment-Naive: Cirrhotic

Table 38 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 4, treatment-naive patients with cirrhosis. (4) SOF24 + RBV24 was associated with an increase in health (1.600 QALY) and cost ($95,194), resulting in an ICUR of $59,492 per QALY compared with PR therapy.

Table 38: Results of Base-Case Deterministic Analysis (Genotype 4: Treatment-Naive Cirrhotic Patients) With Pegylated Interferon Plus Ribavirin as a Reference						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$120,087	8.608	-	-	-	$11,970
(4) SOF24 + RBV24	$215,281	10.208	$95,194	1.600	$59,492	$59,492

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.

4.1.22 Genotype 4: Treatment-Experienced Patients: Non-cirrhotic

Table 39 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 4, treatment-experienced non-cirrhotic patients, when the baseline fibrosis distribution is applied. As noted earlier, So12 PR12, which is indicated for treatment of genotype 4 infection, could not be included in the cost effectiveness analyses as there were insufficient subgroup data by cirrhosis status to include this regimen in the cirrhosis and non-cirrhosis NMAs in the Clinical Review.

The interferon-free regimens are more costly but more effective than no treatment. (4) SOF24 + RBV24 was the most expensive treatment ($201,763.

(4) SOF24 + RBV24 was the most effective treatment in terms of total QALY (11.503 QALY) generated, and was associated with an increase in health (1.907 QALY) and cost ($97,095), resulting in an ICUR of $50,913 per QALY compared with **no treatment**.

Table 39: Results of Base-Case Deterministic Analysis (Genotype 4: Treatment-Experienced Non-cirrhotic Patients) With No Treatment as Reference

Treatment	Total Cost	Total QALYs	Versus No Treatment		
			Incremental Cost	Incremental QALYs	ICUR
(0) no treatment	$104,668	9.596	-	-	-
(4) SOF24 + RBV24	$201,763	11.503	$97,095	1.907	$50,913

ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.23 Genotype 4: Treatment-Experienced Patients: Non-cirrhotic: By Fibrosis Stage

Table 40 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 4, treatment-experienced non-cirrhotic patients using **no treatment** as a reference by fibrosis stages.

Table 40: Results of Base-Case Deterministic Analysis (Genotype 4: Treatment-Experienced Non-cirrhotic Patients) by Fibrosis Stages

Fibrosis Stage, Treatment	Total Cost	Total QALYs	Versus No Treatment		
			Incremental Cost	Incremental QALYs	ICUR
F0					
(0) no treatment	$106,540	10.699	-	-	-
(4) SOF24 + RBV24	$202,082	11.694	$95,542	0.995	$96,056
F1					
(0) no treatment	$106,094	10.428	-	-	-
(4) SOF24 + RBV24	$202,008	11.648	$95,914	1.220	$78,634
F2					
(0) no treatment	$104,837	9.724	-	-	-
(4) SOF24 +	$201,787	11.527	$96,951	1.803	$53,784

Table 40: Results of Base-Case Deterministic Analysis (Genotype 4: Treatment-Experienced Non-cirrhotic Patients) by Fibrosis Stages					
Fibrosis Stage, Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**		
			Incremental Cost	**Incremental QALYs**	**ICUR**
RBV24					
F3					
(0) no treatment	$103,259	8.723	-	-	-
(3) SOF12 + RBV12	$148,528	10.806	$45,269	2.083	$21,734
(4) SOF24 + RBV24	$201,531	11.350	$98,271	2.627	$37,410

F0 = No fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis; ICUR=incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.1.24 Genotype 4: Treatment-Experienced: Cirrhotic

Table 41 summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 4, treatment-experienced patients with cirrhosis. (4) SOF24 + RBV24 was associated with an increase in health (3.050 QALY) and cost ($113,787), resulting in an ICUR of $37,303 per QALY compared with **no treatment**.

Table 41: Results of Base-Case Deterministic Analysis (Genotype 4: Treatment-Experienced: Cirrhotic Patients) With No treatment as a Reference					
Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**		
			Incremental Cost	**Incremental QALYs**	**ICUR**
(0) no treatment	$101,355	7.043	-	-	-
(4) SOF24 + RBV24	$215,142	10.093	$113,787	3.050	$37,303

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.

4.2 Exploratory Analyses

4.2.1 Exploratory Analysis for One-Time Reinfection

To measure the impact of one-time reinfection in the model, we assumed in the analysis that the HCV reinfection rate among active IDUs was 2.4 per 100 person-years,[40] and the proportion of active IDUs was assumed to be between 5% (clinical opinion) to 21.7%.[1] We further assumed that once patients were reinfected with HCV, the patients will lose the benefit of achieving SVR in the model. Table 42 summarizes the results.

The cost-effectiveness results did not change significantly. The main conclusion for all groups remains unchanged.

Table 42: Results of Exploratory Analysis (One-Time Reinfection)			
Genotype 1 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,904 to $104,904	9.734 to 9.734	-
(1) PR48	$114,133 to $114,135	10.838 to 10.839	-
(46) B24 PR28-48 RGT	$135,219 to $135,224	11.369 to 11.370	$39,712 to $39,715
(42) Si12 PR24-48 RGT	$136,771 to $136,776	11.448 to 11.449	$37,113 to $37,116
(32) T12 PR24-48 RGT q8	$137,383 to $137,388	11.399 to 11.400	$41,444 to $41,448
(14) PAR/RIT12 + OMB12 + DAS12	$143,381 to $143,387	11.834 to 11.835	$29,366 to $29,369
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$146,023 to $146,029	11.840 to 11.841	$31,827 to $31,830
(40) So12 PR12	$146,141 to $146,147	11.650 to 11.650	$39,423 to $39,468
(41) So12 PR24-48 RGT	$150,971 to $150,976	11.588 to 11.589	$49,117 to $49,121
(6) SOF12 + LDV12	$152,764 to $152,770	11.856 to 11.857	$37,949 to $37,952
(5) SIM12 + SOF12	$178,357 to $178,363	11.699 to 11.700	$74,593 to $74,597
(72) SOF12+ SIM12+RBV12	$182,384 to $182,390	11.654 to 11.655	$83,642 to $83,645
(4) SOF24 + RBV24	$201,980 to $201,985	11.496 to 11.497	$133,507 to $133,510
Genotype 1 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$120,139 to $120,140	8.658 to 8.658	-
(42) Si12 PR24-48 RGT	$149,011 to $149,012	9.556 to 9.557	$32,126 to $32,140
(32) T12 PR24-48 RGT q8	$153,580 to $153,580	9.219 to 9.219	$59,630 to $59,651
(46) B24 PR28-48 RGT	$160,651 to $160,651	8.188 to 8.189	Dominated
(40) So12 PR12	$160,814 to $160,815	10.008 to 10.009	$30,119 to $30,130
(6) SOF12 + LDV12	$169,482 to $169,483	10.536 to 10.537	$26,265 to $26,274
(5) SIM12 + SOF12	$193,470 to $193,471	10.211 to 10.212	$47,213 to $47,231
(4) SOF24 + RBV24	$214,698 to $214,699	9.635 to 9.636	$96,736 to $96,775
Genotype 1 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,668 to $104,668	9.596 to 9.596	-
(1) PR48	$118,321 to $118,323	10.281 to 10.282	-
(42) Si12 PR24-48 RGT	$138,661 to $138,665	11.168 to 11.169	$22,931 to $22,934
(39) T12 PR48 q8	$142,466 to $142,470	11.393 to 11.394	$21,713 to $21,715
(14) PAR/RIT12 + OMB12 + DAS12	$142,919 to $142,925	11.867 to 11.868	$15,509 to $15,512
(74) B32 PR36-48 RGT	$143,265 to $143,269	11.122 to 11.122	$29,663 to $29,695
(68) Si12 PR48	$143,842 to $143,846	11.405 to 11.406	$22,705 to $22,708
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,745 to $145,751	11.897 to 11.898	$16,970 to $16,973
(40) So12 PR12	$150,155 to $150,160	11.470 to 11.471	$26,773 to $26,776
(6) SOF12 + LDV12	$154,323 to $154,329	11.760 to 11.761	$24,342 to $24,345
(72) SOF12+ SIM12+RBV12	$186,876 to $186,880	11.046 to 11.046	$89,617 to $89,732
(5) SIM12 + SOF12	$189,079 to $189,081	10.280 to 10.280	Dominated

Table 42: Results of Exploratory Analysis (One-Time Reinfection)			
Genotype 1 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$119,828 to $119,828	7.924 to 7.924	-
(42) Si12 PR24-48 RGT	$148,780 to $148,780	9.325 to 9.326	$20,651 to $20,665
(74) B32 PR36-48 RGT	$153,491 to $153,492	8.758 to 8.758	$40,364 to $40,365
(39) T12 PR48 q8	$153,690 to $153,691	9.045 to 9.046	$30,181 to $30,208
(68) Si12 PR48	$154,911 to $154,912	8.878 to 8.879	$36,737 to $36,776
(40) So12 PR12	$162,498 to $162,499	8.941 to 8.941	$41,957 to $41,958
(10) SOF12 + LDV12 + RBV12	$172,975 to $172,976	9.932 to 9.933	$26,455 to $26,468
(5) SIM12 + SOF12	$193,051 to $193,052	9.964 to 9.965	$35,877 to $35,894
(7) SOF24 + LDV24	$234,377 to $234,378	9.886 to 9.886	$58,384 to $58,384
Genotype 2 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(70) PR24	$99,905 to $99,910	11.531 to 11.532	-
(0) no treatment	$104,904 to $104,904	9.734 to 9.734	-
(3) SOF12 + RBV12	$143,956 to $143,962	11.748 to 11.748	$203,002 to $203,939
(40) So12 PR12	$145,732 to $145,738	11.697 to 11.698	$276,065 to $276,069
Genotype 2 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(70) PR24	$112,766 to $112,767	9.383 to 9.383	-
(3) SOF12 + RBV12	$159,539 to $159,540	10.180 to 10.181	$58,613 to $58,686
Genotype 2 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$104,668 to $104,668	9.600 to 9.600	-
(3) SOF12 + RBV12	$144,025 to $144,031	11.750 to 11.750	$18,305 to $18,308
(40) So12 PR12	$145,462 to $145,467	11.690 to 11.690	$19,518 to $19,521
Genotype 2 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(3) SOF12 + RBV12	$159,346 to $159,347	9.760 to 9.761	$21,336 to $21,344
(40) So12 PR12	$160,862 to $160,863	10.307 to 10.308	$18,226 to $18,231
(73) SOF16 + RBV16	$177,501 to $177,502	9.894 to 9.895	$26,700 to $26,709
Genotype 3 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,183 to $104,183	9.314 to 9.314	-
(1) PR48	$110,388 to $110,392	11.156 to 11.156	-
(4) SOF24 + RBV24	$199,739 to $199,745	11.733 to 11.734	$154,588 to $154,858
Genotype 3 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$120,843 to $120,843	9.334 to 9.334	-
(4) SOF24 + RBV24	$215,436 to $215,437	10.360 to 10.361	$92,107 to $92,197

Table 42: Results of Exploratory Analysis (One-Time Reinfection)			
Genotype 3 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$103,932 to $103,932	9.167 to 9.167	-
(1) PR48	$112,302 to $112,305	10.878 to 10.879	$4,889 to $4,893
(40) So12 PR12	$149,250 to $149,255	11.509 to 11.510	$19,342 to $19,352
(4) SOF24 + RBV24	$200,326 to $200,331	11.636 to 11.637	$39,026 to $39,044
Genotype 3 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$103,932 to $103,932	9.167 to 9.167	-
(1) PR48	$112,302 to $112,305	10.878 to 10.879	$4,889 to $4,893
(40) So12 PR12	$149,250 to $149,255	11.509 to 11.510	$19,342 to $19,352
(4) SOF24 + RBV24	$200,326 to $200,331	11.636 to 11.637	$39,026 to $39,044
Genotype 4 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,904 to $104,904	9.734 to 9.734	-
(1) PR48	$111,497 to $111,501	11.157 to 11.157	-
(4) SOF24 + RBV24	$201,518 to $201,523	11.552 to 11.553	$227,326 to $227,905
Genotype 4 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$120,087 to $120,087	8.607 to 8.608	-
(4) SOF24 + RBV24	$215,280 to $215,281	10.207 to 10.208	$59,496 to $59,496
Genotype 4 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$104,668 to $104,668	9.596 to 9.596	-
(4) SOF24 + RBV24	$201,765 to $201,770	11.502 to 11.503	$50,916 to $50,945
Genotype 4 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(4) SOF24 + RBV24	$215,141 to $215,142	10.092 to 10.093	$37,307 to $37,319

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin.

4.2.2 Exploratory Analysis for Regimens Without Price Information

In this exploratory analysis, we assessed the cost-effectiveness of daclatasavir-based regimens by assuming the price of these regimens (DAC24 + ASU24 and DAC12 + SOF12) ranged between $55,860 (cost of PAR/RIT12 + OMB12 + DAS12) to $67,000 (cost of SOF12 + LDV12).

Table 43 summarizes the outcomes associated with the exploratory analysis. In both genotype 1 treatment-naive and treatment-experienced non-cirrhotic patients, both (17) DAC24 + ASU24 and (19) DAC12 + SOF12 were dominated by (14) PAR/RIT12 + OMB12 + DAS12.

For genotype 1 naive patients with cirrhosis, (17) DAC24 + ASU24 became the most cost-effective treatment. (17) DAC24 + ASU24 was associated with an increase in health (1.669 QALY) and cost ($38,861 to $49,687), resulting in an ICUR of $23,279 to $29,764 per QALY, compared with PR therapy.

For genotype 1 experienced patients with cirrhosis, (17) DAC24 + ASU24 became the most cost-effective treatment, followed by (18) DAC24 + ASU24 + PR24. (17) DAC24 + ASU24 was associated with an increase in health (2.279 QALY) and cost ($39,193 to $50,036), resulting in an ICUR of $17,194 to $21,951 per QALY, compared with PR therapy. (18) DAC24 + ASU24 + PR24 was associated with an increase in health (2.429 QALY) and cost ($48,622 to $59,453), resulting in an ICUR of $20,014 to $24,472 per QALY compared with PR therapy.

For genotype 3 naive non-cirrhotic patients, (19) DAC12 + SOF12 became the most cost-effective treatment. (19) DAC12 + SOF12 was associated with an increase in health (0.675 QALY) and cost ($31,676 to $42,421), resulting in an ICUR of $46,913 to $62,828 per QALY, compared with PR therapy. Similarly, for genotype 3 experienced non-cirrhotic patient, (19) DAC12 + SOF12 became the most cost-effective treatment. (19) DAC12 + SOF12 was associated with an increase in health (2.612 QALY) and cost ($39,151 to $50,043), resulting in an ICUR of $14,986 to $19,155 per QALY, compared with no treatment.

For genotype 4 experienced non-cirrhotic patient, (18) DAC24 + ASU24 + PR24 became the most cost-effective treatment. (18) DAC24 + ASU24 + PR24 was associated with an increase in health (2.194 QALY) and cost ($47,843 to $58,679), resulting in an ICUR of $21,810 to $26,750 per QALY, compared with no treatment. Similarly, for genotype 4 experienced patients with cirrhosis, (18) DAC24 + ASU24 + PR24 also became the most cost-effective treatment. (18) DAC24 + ASU24 + PR24 was associated with an increase in health (3.359 QALY) and cost ($67,134 to $77,966), resulting in an ICUR of $19,989 to $23,214 per QALY, compared with no treatment.

Table 43: Results of Exploratory Analysis (Regimens Without Price Information)

Treatment	Total Cost	Total QALYs	Versus PR Alone			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
Genotype 1 Treatment-Naive Non-cirrhotic						
(0) no treatment	$104,904	9.734	-	-	-	-
(1) PR48	$114,132	10.839	-	-	-	$8,353
(14) PAR/RIT12 + OMB12 + DAS12	$143,379	11.835	$29,247	0.996	$29,354	$29,354
(6) SOF12 + LDV12	$152,762	11.857	$38,631	1.018	$37,951	$435,528
Dominated or Extendedly Dominated[a] Treatments						
(46) B24 PR28-48 RGT	$135,218	11.370	$21,086	0.531	$39,710	ext. dominated
(42) Si12 PR24-48 RGT	$136,770	11.449	$22,638	0.610	$37,106	ext. dominated
(32) T12 PR24-48 RGT q8	$137,381	11.400	$23,250	0.561	$41,452	dominated
(19) DAC12 + SOF12	$142,507 to $153,261	11.800	$28,375 to $39,130	0.961	$29,528 to $40,720	ext. dominated
(17) DAC24 + ASU24	$143,957 to $154,796	11.711	$29,825 to $40,664	0.872	$34,203 to $46,633	dominated
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$146,021	11.841	$31,890	1.002	$31,823	ext. dominated
(40) So12 PR12	$146,140	11.651	$32,008	0.812	$39,431	dominated

Table 43: Results of Exploratory Analysis (Regimens Without Price Information)						
(41) So12 PR24-48 RGT	$150,969	11.589	$36,837	0.750	$49,113	dominated
(5) SIM12 + SOF12	$178,356	11.700	$64,224	0.861	$74,582	dominated
(72) SOF12+ SIM12+RBV12	$182,383	11.655	$68,251	0.816	$83,618	dominated
(4) SOF24 + RBV24	$201,979	11.497	$87,847	0.658	$133,509	dominated
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 1 Treatment-Naive Cirrhotic						
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$120,140	8.659	-	-	-	$11,628
(17) DAC24 + ASU24	$159,001 to $169,827	10.328	$38,861 to $49,687	1.669	$23,279 to $29,764	$23,279 to dominated
(6) SOF12 + LDV12	$169,483	10.538	$49,344	1.879	$26,261	$50,013
Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$149,012	9.557	$28,872	0.899	$32,123	ext. dominated
(32) T12 PR24-48 RGT q8	$153,580	9.219	$33,441	0.561	$59,622	dominated
(46) B24 PR28-48 RGT	$160,651	8.189	$40,512	–0.470	–$86,232	dominated
(40) So12 PR12	$160,816	10.009	$40,676	1.351	$30,115	dominated
(5) SIM12 + SOF12	$193,471	10.212	$73,332	1.553	$47,208	dominated
(4) SOF24 + RBV24	$214,699	9.636	$94,559	0.978	$96,723	dominated
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 1 Treatment-Experienced Non-cirrhotic						
(0) no treatment	$104,668	9.596	-	-	-	-
(1) PR48	$118,321	10.282	-	-	-	ext. dominated
(14) PAR/RIT12 + OMB12 + DAS12	$142,917	11.868	$24,597	1.586	$15,506	$16,836
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,743	11.898	$27,422	1.616	$16,965	$93,872
Other Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$138,660	11.169	$20,339	0.887	$22,918	ext. dominated
(39) T12 PR48 q8	$142,464	11.394	$24,143	1.113	$21,702	ext. dominated
(74) B32 PR36-48 RGT	$143,264	11.122	$24,943	0.841	$29,675	dominated
(68) Si12 PR48	$143,840	11.406	$25,519	1.124	$22,702	dominated

Table 43: Results of Exploratory Analysis (Regimens Without Price Information)						
(17) DAC24 + ASU24	$145,857 to $156,713	11.467	$27,537 to $38,392	1.186	$23,227 to $32,383	abs. dominated
(40) So12 PR12	$150,153	11.471	$31,833	1.189	$26,770	dominated
(18) DAC24 + ASU24 + PR24	$153,810 to $164,655	11.622	$35,489 to $46,334	1.340	$26,477 to $34,568	dominated
(6) SOF12 + LDV12	$154,321	11.761	$36,001	1.480	$24,329	dominated
(72) SOF12+ SIM12+RBV12	$186,875	11.046	$68,554	0.765	$89,659	dominated
(5) SIM12 + SOF12	$189,079	10.280	$70,758	–0.001	–$53,919,201	dominated
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 1 Treatment-Experienced Cirrhotic						
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$119,828	7.924	-	-	-	ext. dominated
(17) DAC24 + ASU24	$159,021 to $169,863	10.204	$39,193 to $50,036	2.279	$17,194 to $21,951	$18,245 to $21,673
(18) DAC24 + ASU24 + PR24	$168,449 to $179,281	10.354	$48,622 to $59,453	2.429	$20,014 to $24,472	$62,791 to $62,863
Dominated or Extendedly Dominated Treatments						
(42) Si12 PR24-48 RGT	$148,780	9.326	$28,953	1.402	$20,655	ext. dominated
(74) B32 PR36-48 RGT	$153,492	8.758	$33,664	0.834	$40,357	dominated
(39) T12 PR48 q8	$153,691	9.046	$33,863	1.122	$30,190	dominated
(68) Si12 PR48	$154,912	8.879	$35,084	0.954	$36,757	dominated
(40) So12 PR12	$162,499	8.941	$42,671	1.017	$41,954	dominated
(10) SOF12 + LDV12 + RBV12	$172,976	9.933	$53,148	2.009	$26,456	dominated
(5) SIM12 + SOF12	$193,052	9.966	$73,225	2.041	$35,870	dominated
(7) SOF24 + LDV24	$234,378	9.887	$114,550	1.962	$58,371	dominated
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 3 Treatment-Naive Non-cirrhotic						
(0) no treatment	$104,183	9.314	-	-	-	-
(1) PR48	$110,387	11.156	-	-	-	$3,367
(19) DAC12 + SOF12	$142,062 to $152,808	11.832	$31,676 to $42,421	0.675	$46,913 to $62,828	$46,913 to $62,828
Dominated or Extendedly Dominated[a] Treatments						
(4) SOF24 + RBV24	$199,738	11.734	$89,351	0.578	$154,599	dominated

Table 43: Results of Exploratory Analysis (Regimens Without Price Information)						
Treatment	Total Cost	Total QALYs	Versus No Treatment			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
Genotype 3 Treatment-Experienced Non-cirrhotic						
(0) no treatment	$103,932	9.167	-	-	-	-
(1) PR48	$112,301	10.879	$8,368	1.712	$4,888	$4,888
(19) DAC12 + SOF12	$143,083 to $153,975	11.780	$39,151 to $50,043	2.612	$14,986 to $19,155	$34,187 to $46,284
Dominated or Extendedly Dominated[a] Treatments						
(40) So12 PR12	$149,249	11.510	$45,316	2.343	$19,339	dominated
(4) SOF24 + RBV24	$200,324	11.637	$96,392	2.470	$39,025	dominated
Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 4 Treatment-Experienced Non-cirrhotic						
(0) no treatment	$104,668	9.596	-	-	-	-
(18) DAC24 + ASU24 + PR24	$152,511 to $163,348	11.790	$47,843 to $58,679	2.194	$21,810 to $26,750	$21,810 to $26,750
Dominated or Extendedly Dominated[a] Treatments						
(4) SOF24 + RBV24	$201,763	11.503	$97,095	1.907	$50,913	dominated
Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 4 Treatment-Experienced Cirrhotic						
(0) no treatment	$101,355	7.043	-	-	-	-
(18) DAC24 + ASU24 + PR24	$168,489 to $179,321	10.402	$67,134 to $77,966	3.359	$19,989 to $23,214	$19,989 to $23,214
Dominated or Extendedly Dominated[a] Treatments						
(4) SOF24 + RBV24	$215,142	10.093	$113,787	3.050	$37,303	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.2.3 Exploratory Analysis for SOF8+LDV8 in Genotype 1-Naive Non-cirrhotic Patients

Health Canada has a special indication for treatment (8) SOF8+LDV8. That is, the treatment should be used only for treatment naive patients without cirrhosis and with HCV RNA < 6 million IU/mL. In this exploratory analysis, we included (8) SOF8+LDV8 in the analysis.
Table 44 summarizes the outcomes associated with the exploratory analysis. For genotype 1 treatment-naive non-cirrhotic patients, (8) SOF8+LDV8 became the most cost-effective treatment. (8) SOF8+LDV8 was associated with an increase in health (0.987 QALY) and cost ($17,066), resulting in an ICUR of $17,287 per QALY, compared with PR alone.

Table 44: Results of Exploratory Analysis (Genotype 1 Treatment-Naive Non-cirrhotic Patients) With SOF8+LDV8 Included						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
(0) no treatment	$104,904	9.734	-	-	-	-
(1) PR48	$114,105	10.842	-	-	-	$8,304
(8) SOF8 + LDV8	$131,171	11.829	$17,066	0.987	$17,287	$17,287
(6) SOF12 + LDV12	$152,762	11.857	$21,591	0.027	$786,547	$786,547
Dominated or Extendedly Dominated[a] Treatments						
(46) B24 PR28-48 RGT	$135,177	11.375	$21,072	0.533	$39,550	dominated
(42) Si12 PR24-48 RGT	$136,735	11.453	$22,629	0.611	$37,028	dominated
(32) T12 PR24-48 RGT q8	$137,398	11.398	$23,293	0.556	$41,917	dominated
(14) PAR/RIT12 + OMB12 + DAS12	$143,403	11.832	$29,298	0.990	$29,585	ext. dominated
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$146,036	11.839	$31,931	0.997	$32,023	ext. dominated
(40) So12 PR12	$146,378	11.622	$32,273	0.780	$41,383	dominated
(41) So12 PR24-48 RGT	$150,912	11.596	$36,807	0.754	$48,839	dominated
(5) SIM12 + SOF12	$178,462	11.687	$64,357	0.845	$76,151	dominated
(72) SOF12+ SIM12+RBV12	$182,648	11.623	$68,543	0.781	$87,741	dominated
(4) SOF24 + RBV24	$202,019	11.492	$87,914	0.650	$135,266	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.2.4 Exploratory Analysis for PAR/RIT12+OMB12+DAS12+RBV12 in Genotype 1 Cirrhotic Patients

Table 45 summarizes the outcomes associated with the exploratory analysis in which PAR/RIT12 + OMB12 + DAS12 + RBV12 was incorporated for patients with genotype 1 infection and cirrhosis, based on the results of the TURQUOISE II trial. For genotype 1 treatment-naive patients with cirrhosis, (15) PAR/RIT12 + OMB12 + DAS12 + RBV12 became the most cost-effective treatment. (15) PAR/RIT12 + OMB12 + DAS12 + RBV12 was associated with an increase in health (1.847 QALY) and cost ($42,577), resulting in an ICUR of $23,047 per QALY, compared with PR alone. Similarly, in the genotype 1 treatment-experienced cirrhotic patient, (15) PAR/RIT12 + OMB12 + DAS12 + RBV12 also became the most cost-effective treatment. (15) PAR/RIT12 + OMB12 + DAS12 + RBV12 was associated with an increase in health (2.430 QALY) and cost ($42,928), resulting in an ICUR of $17,669, per QALY compared with PR alone.

Table 45: Results of Base-Case Deterministic Analysis (Genotype 1 Cirrhotic Patients) With PAR/RIT12+OMB12+DAS12+RBV12 Included						
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 1 Treatment-Naive Cirrhotic						
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$120,119	8.639	-	-	-	$11,759
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$162,696	10.486	$42,577	1.847	$23,047	$23,047
(6) SOF12 + LDV12	$169,479	10.533	$49,360	1.895	$26,055	$144,200
Dominated or Extendedly Dominated[a] Treatments						
(42) Si12 PR24-48 RGT	$148,970	9.516	$28,851	0.877	$32,881	ext. dominated
(32) T12 PR24-48 RGT q8	$153,562	9.202	$33,442	0.563	$59,438	dominated
(46) B24 PR28-48 RGT	$160,658	8.195	$40,538	-0.444	-$91,292	dominated
(40) So12 PR12	$160,838	10.032	$40,719	1.393	$29,235	ext. dominated
(5) SIM12 + SOF12	$193,483	10.223	$73,364	1.585	$46,300	dominated
(4) SOF24 + RBV24	$214,667	9.604	$94,547	0.965	$97,936	dominated
Treatment	**Total Cost**	**Total QALYs**	**Versus PR Alone**			
			Incremental Cost	**Incremental QALYs**	**ICUR**	**Sequential ICUR**
Genotype 1 Treatment-Experienced Cirrhotic						
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$119,808	7.906	-	-	-	ext. dominated
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$162,736	10.335	$42,928	2.430	$17,669	$17,669
Dominated or Extendedly Dominated Treatments						
(42) Si12 PR24-48 RGT	$148,728	9.274	$28,919	1.369	$21,130	ext. dominated
(74) B32 PR36-48 RGT	$153,490	8.756	$33,681	0.851	$39,591	dominated
(39) T12 PR48 q8	$153,647	9.004	$33,839	1.098	$30,811	dominated
(68) Si12 PR48	$154,865	8.834	$35,057	0.928	$37,780	dominated
(40) So12 PR12	$162,461	8.904	$42,653	0.999	$42,715	dominated
(10) SOF12 + LDV12 + RBV12	$173,000	9.957	$53,191	2.051	$25,932	dominated
(5) SIM12 + SOF12	$193,060	9.973	$73,252	2.068	$35,428	dominated
(7) SOF24 + LDV24	$234,399	9.907	$114,590	2.002	$57,248	dominated

ext = extendedly; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PR = pegylated interferon plus ribavirin. Refer to Table 2 for treatment description.
[a] Extendedly dominated = the combination of two other alternatives dominated the treatment.

4.2.5 Exploratory Analysis incorporating BOSON study results for Genotype 3 Patients

In the exploratory analysis incorporating data from the BOSON study, (40) So12 PR12 became the most cost-effective treatment for genotype 3 treatment-naive non-cirrhotic patients. (40)

So12 PR12 was associated with an increase in health (0.497 QALY) and cost ($35,297), resulting in an ICUR of $70,972 per QALY, compared with PR alone. For genotype 3 treatment-naive patients with cirrhosis, (40) So12 PR12 also became the most cost-effective treatment. (40) So12 PR12 was associated with an increase in health (0.969 QALY) and cost ($40,268), resulting in an ICUR of $41,574 per QALY, compared with PR alone.

For genotype 3 treatment-experienced (non-cirrhotic and cirrhotic) patients, the main conclusions remain unchanged for both groups.

Table 46: Results of Base-Case Exploratory Analysis (Genotype 3) for So12 PR12

Fibrosis Stage, Treatment	Total Cost	Total QALYs	Versus PR			
			Incremental Cost	Incremental QALYs	ICUR	Sequential ICUR
Treatment-Naive Non-cirrhotic						
(0) no treatment	$104,183	9.314	-	-	-	-
(1) PR48	$110,366	11.159	-	-	-	$3,350
(40) So12 PR12	$145,663	11.657	$35,297	0.497	$70,972	$70,972
(4) SOF24 + RBV24	$199,768	11.730	$89,402	0.570	$156,764	$741,634
Treatment-Naive Cirrhotic						
(0) no treatment	$101,355	7.043	-	-	-	-
(1) PR48	$120,845	9.337	-	-	-	$8,498
(40) So12 PR12	$161,113	10.305	$40,268	0.969	$41,574	$41,574
Dominated Treatments						
(4) SOF24 + RBV24	$215,365	10.291	$114,010	3.248	$99,060	Dominated
Treatment-Experienced Non-cirrhotic						
(0) no treatment	$103,932	9.167	-	-	-	-
(1) PR48	$112,301	10.879	$8,368	1.712	$4,888	$4,888
(40) So12 PR12	$147,652	11.763	$43,720	2.596	$16,841	$39,990
Dominated Treatments						
(4) SOF24 + RBV24	$200,554	11.601	$96,622	2.433	$39,705	Dominated
Treatment-Experienced Cirrhotic						
(0) no treatment	$101,355	7.043				
(1) PR48	$120,879	8.934	$19,524	1.891	$10,323	$10,323
(40) So12 PR12	$163,633	10.068	$62,278	3.025	$20,586	$37,701
Dominated Treatments						
(4) SOF24 + RBV24	$214,711	9.666	$113,356	2.623	$43,219	Dominated

ICUR=incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.3 Deterministic Sensitivity Analysis

4.3.1 Treatment Efficacy (Network Meta-analysis Results)

To further measure the impact treatment effect estimates used in the model, the parameters were varied by the 95% Crl generated by the NMA, as indicated in Table 5.The results of the sensitivity analysis are presented in Table 47.

In this analysis, the cost-effectiveness results changed significantly. In the genotype 1 treatment-naive non-cirrhotic group, the ICUR varied from $25,988 to $92,392 for the most cost-effective treatment ((14) PAR/RIT12 + OMB12 + DAS12) when compared with PR, which may not be considered economically attractive. The main conclusions for the genotype 1 treatment-naive cirrhotic and treatment-experienced non-cirrhotic groups remain unchanged. For the genotype 1 treatment-experienced cirrhotic group, the ICUR varied from $11,517 to $99,452 for the most cost-effective treatment ((42) Si12 PR24-48 RGT) when compared with PR, which may not be considered economically attractive. The main conclusions for the genotype 2, 3 and 4 groups remain unchanged.

Table 47: Results of Sensitivity Analysis On-Treatment Efficacy

Genotype 1 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,904	9.734	-
(1) PR48	$114,132	10.839	-
(46) B24 PR28-48 RGT	$134,674 to $137,449	11.101 to 11.436	$34,428 to $88,977
(42) Si12 PR24-48 RGT	$135,116 to $138,279	11.267 to 11.648	$25,930 to $56,386
(32) T12 PR24-48 RGT q8	$135,600 to $139,423	11.154 to 11.615	$27,680 to $80,353
(14) PAR/RIT12 + OMB12 + DAS12	$142,565 to $148,573	11.212 to 11.933	$25,988 to $92,392
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,490 to $147,732	11.636 to 11.905	$29,419 to $42,175
(40) So12 PR12	$145,733 to $150,426	11.136 to 11.700	$36,721 to $122,144
(41) So12 PR24-48 RGT	$150,178 to $155,082	11.094 to 11.684	$42,647 to $160,633
(6) SOF12 + LDV12	$152,762 to $154,210	11.683 to 11.857	$37,951 to $47,481
(5) SIM12 + SOF12	$176,905 to $187,098	10.650 to 11.874	Dominated to $60,629
(72) SOF12+ SIM12+RBV12	$180,351 to $190,290	10.706 to 11.899	Dominated to $62,459
Genotype 1 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355	7.043	-
(1) PR48	$120,140	8.659	-
(42) Si12 PR24-48 RGT	$148,139 to $149,907	8.702 to 10.435	$16,761 to $637,365
(32) T12 PR24-48 RGT q8	$152,510 to $154,613	8.191 to 10.212	Dominated to $22,195
(46) B24 PR28-48 RGT	$159,997 to $162,011	7.560 to 9.495	Dominated to $50,031
(40) So12 PR12	$159,554 to $161,113	8.756 to 10.305	$24,883 to $403,343
(6) SOF12 + LDV12	$168,772 to $169,494	9.831 to 10.548	$26,126 to $41,489
(5) SIM12 + SOF12	$191,758 to $193,842	8.510 to 10.580	Dominated to $38,360
(4) SOF24 + RBV24	$213,141 to $215,567	8.106 to 10.489	Dominated to $52,136

Table 47: Results of Sensitivity Analysis On-Treatment Efficacy			
Genotype 1 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,668	9.596	-
(1) PR48	$118,321	10.282	-
(42) Si12 PR24-48 RGT	$135,935 to $142,307	10.697 to 11.522	$14,206 to $57,711
(39) T12 PR48 q8	$140,138 to $145,132	11.048 to 11.696	$15,421 to $35,003
(14) PAR/RIT12 + OMB12 + DAS12	$142,389 to $145,393	11.549 to 11.936	$14,548 to $21,369
(74) B32 PR36-48 RGT	$139,948 to $146,894	10.652 to 11.552	$17,023 to $77,261
(68) Si12 PR48	$141,248 to $147,604	10.917 to 11.743	$15,695 to $46,098
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$145,508 to $147,876	11.623 to 11.928	$16,511 to $22,036
(40) So12 PR12	$147,128 to $153,856	10.993 to 11.861	$18,238 to $49,939
(6) SOF12 + LDV12	$153,152 to $156,901	11.429 to 11.912	$21,360 to $33,636
(72) SOF12+ SIM12+RBV12	$180,266 to $196,466	9.809 to 11.899	Dominated to $38,307
(5) SIM12 + SOF12	$177,300 to $193,470	9.714 to 11.800	Dominated to $38,852
Genotype 1 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355	7.043	-
(1) PR48	$119,828	7.924	-
(42) Si12 PR24-48 RGT	$147,637 to $150,024	8.204 to 10.546	$11,517 to $99,452
(74) B32 PR36-48 RGT	$152,450 to $155,111	7.757 to 10.314	Dominated to $14,764
(39) T12 PR48 q8	$152,730 to $155,074	8.123 to 10.375	$14,383 to $165,822
(68) Si12 PR48	$153,864 to $156,417	7.872 to 10.325	Dominated to $15,240
(40) So12 PR12	$160,948 to $164,231	7.401 to 10.662	Dominated to $16,220
(10) SOF12 + LDV12 + RBV12	$171,976 to $173,680	8.939 to 10.633	$19,883 to $51,370
(5) SIM12 + SOF12	$191,359 to $193,674	8.284 to 10.583	$27,771 to $199,113
(7) SOF24 + LDV24	$232,679 to $235,183	8.218 to 10.678	$41,890 to $384,306
Genotype 2 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(70) PR24	$99,904	11.532	-
(0) no treatment	$104,904	9.734	-
(3) SOF12 + RBV12	$143,954 to $144,379	11.698 to 11.749	$203,289 to $268,442
(40) So12 PR12	$145,731 to $154,648	10.627 to 11.698	Dominated to $276,114
Genotype 2 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355	7.043	-
(70) PR24	$112,767	9.384	-
(3) SOF12 + RBV12	$158,784 to $159,740	9.430 to 10.379	$47,166 to $999,719
Genotype 2 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**

Table 47: Results of Sensitivity Analysis On-Treatment Efficacy			
(0) no treatment	$104,668	9.596	-
(3) SOF12 + RBV12	$144,023 to $144,232	11.726 to 11.753	$18,247 to $18,575
(40) So12 PR12	$145,460 to $146,176	11.596 to 11.689	$19,494 to $20,752
Genotype 2 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355	7.043	
(3) SOF12 + RBV12	$158,809 to $159,774	9.227 to 10.185	$18,594 to $26,313
(40) So12 PR12	$160,274 to $160,863	9.723 to 10.308	$18,226 to $21,986
(73) SOF16 + RBV16	$176,636 to $178,017	9.038 to 10.405	$22,804 to $37,745
Genotype 3 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,183	9.314	-
(1) PR48	$110,387	11.156	-
(4) SOF24 + RBV24	$199,459 to $201,396	11.488 to 11.776	$143,840 to $274,300
Genotype 3 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355	7.043	-
(1) PR48	$120,843	9.335	-
(4) SOF24 + RBV24	$214,672 to $215,567	9.610 to 10.489	$82,064 to $341,283
Genotype 3 Treatment-Experienced non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$103,932	9.167	-
(1) PR48	$112,301	10.879	-
(40) So12 PR12	$146,834 to $154,408	10.693 to 11.893	$15,739 to $33,074
(4) SOF24 + RBV24	$199,309 to $201,844	11.396 to 11.637	$38,614 to $43,934
Genotype 3 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355	7.043	-
(1) PR48	$120,880	8.936	-
(40) So12 PR12	$162,579 to $164,231	9.021 to 10.662	$17,375 to $30,959
(4) SOF24 + RBV24	$214,167 to $215,242	9.131 to 9.661	$43,496 to $54,019
Genotype 4 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,904	9.734	-
(1) PR48	$111,496	11.158	-
(4) SOF24 + RBV24	$199,492 to $206,085	11.003 to 11.797	Dominated to $137,682
Genotype 4 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355	7.043	-
(1) PR48	$120,087	8.608	-
(4) SOF24 + RBV24	$214,084 to $215,567	9.031 to 10.489	$50,765 to $222,004
Genotype 4 Treatment-Experienced Non-cirrhotic			

Table 47: Results of Sensitivity Analysis On-Treatment Efficacy			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$104,668	9.596	-
(4) SOF24 + RBV24	$199,332 to $208,275	10.661 to 11.818	$42,610 to $97,292
Genotype 4 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. no treatment**
(0) no treatment	$101,355	7.043	-
(4) SOF24 + RBV24	$213,395 to $215,583	8.377 to 10.526	$32,793 to $83,995

ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.3.2 Cost of Antiviral Therapy

To measure the impact of the cost of antiviral therapies used in the model, parameters were varied by ± 25%, as indicated in Table 11. Table 48 summarizes the results of the sensitivity analysis.

The cost-effectiveness results changed significantly in this analysis. For the genotype 2 and genotype 4 treatment-naive cirrhotic groups, the generated ICUR for the most cost-effective treatments (genotype 2: (3) SOF12 + RBV12 and genotype 4: (4) SOF24 + RBV24) may be less than $50,000 when compared with PR. The main conclusion for other groups remains unchanged.

Table 48: Results of Sensitivity Analysis on Cost of Antiviral Therapy			
Genotype 1 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,904 to $104,904	9.734 to 9.734	-
(1) PR48	$114,132 to $114,132	10.839 to 10.839	-
(46) B24 PR28-48 RGT	$124,753 to $145,684	11.370 to 11.370	$20,002 to $59,420
(42) Si12 PR24-48 RGT	$125,602 to $147,938	11.449 to 11.449	$18,804 to $55,420
(32) T12 PR24-48 RGT q8	$126,287 to $148,476	11.400 to 11.400	$21,667 to $61,220
(14) PAR/RIT12 + OMB12 + DAS12	$129,628 to $157,130	11.835 to 11.835	$15,559 to $43,171
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$131,593 to $160,449	11.841 to 11.841	$17,427 to $46,225
(40) So12 PR12	$132,191 to $160,089	11.651 to 11.651	$22,240 to $56,597
(41) So12 PR24-48 RGT	$135,952 to $165,987	11.589 to 11.589	$29,093 to $69,140
(6) SOF12 + LDV12	$136,592 to $168,933	11.857 to 11.857	$22,063 to $53,832
(5) SIM12 + SOF12	$156,147 to $200,564	11.700 to 11.700	$48,799 to $100,386
(72) SOF12+ SIM12+RBV12	$159,260 to $205,505	11.655 to 11.655	$55,305 to $111,978
Genotype 1 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$120,140 to $120,140	8.659 to 8.659	-
(42) Si12 PR24-48 RGT	$137,857 to $160,167	9.557 to 9.557	$19,712 to $44,534
(32) T12 PR24-48 RGT q8	$141,322 to $165,839	9.219 to 9.219	$37,765 to $81,474
(46) B24 PR28-48 RGT	$146,354 to $174,949	8.189 to 8.189	Dominated
(40) So12 PR12	$146,883 to $174,749	10.009 to 10.009	$19,799 to $40,430
(6) SOF12 + LDV12	$153,331 to $185,635	10.538 to 10.538	$17,664 to $34,857

Table 48: Results of Sensitivity Analysis on Cost of Antiviral Therapy			
(5) SIM12 + SOF12	$171,288 to $215,654	10.212 to 10.212	$32,927 to $61,487
(4) SOF24 + RBV24	$187,187 to $242,212	9.636 to 9.636	$68,576 to $124,856
Genotype 1 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,668 to $104,668	9.596 to 9.596	-
(1) PR48	$118,321 to $118,321	10.282 to 10.282	-
(42) Si12 PR24-48 RGT	$127,477 to $149,843	11.169 to 11.169	$10,322 to $35,537
(14) PAR/RIT12 + OMB12 + DAS12	$129,167 to $156,668	11.868 to 11.868	$6,838 to $24,179
(39) T12 PR48 q8	$130,098 to $154,831	11.394 to 11.394	$10,591 to $32,833
(68) Si12 PR48	$131,006 to $156,674	11.406 to 11.406	$11,286 to $34,122
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$131,243 to $160,243	11.898 to 11.898	$7,996 to $25,942
(74) B32 PR36-48 RGT	$134,897 to $155,284	11.122 to 11.122	$19,734 to $44,004
(40) So12 PR12	$135,452 to $164,855	11.471 to 11.471	$14,408 to $39,137
(6) SOF12 + LDV12	$137,928 to $170,715	11.761 to 11.761	$13,257 to $35,426
(72) SOF12+ SIM12+RBV12	$163,752 to $209,998	11.046 to 11.046	$59,465 to $119,996
(5) SIM12 + SOF12	$166,870 to $211,287	10.280 to 10.280	Dominated
Genotype 1 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$119,828 to $119,828	7.924 to 7.924	-
(42) Si12 PR24-48 RGT	$137,610 to $159,950	9.326 to 9.326	$12,684 to $28,618
(39) T12 PR48 q8	$141,339 to $166,043	9.046 to 9.046	$19,172 to $41,190
(68) Si12 PR48	$142,093 to $167,731	8.879 to 8.879	$23,314 to $50,161
(40) So12 PR12	$147,815 to $177,183	8.941 to 8.941	$27,519 to $56,397
(74) B32 PR36-48 RGT	$149,723 to $180,075	8.758 to 8.758	$35,845 to $72,239
(10) SOF12 + LDV12 + RBV12	$155,848 to $190,104	9.933 to 9.933	$17,929 to $34,981
(5) SIM12 + SOF12	$170,869 to $215,235	9.966 to 9.966	$24,996 to $46,723
(7) SOF24 + LDV24	$201,838 to $266,918	9.887 to 9.887	$41,778 to $74,932
Genotype 2 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(70) PR24	$99,904 to $99,904	11.532 to 11.532	-
(0) no treatment	$104,904 to $104,904	9.734 to 9.734	-
(3) SOF12 + RBV12	$128,113 to $154,051	11.749 to 11.749	$129,998 to $249,528
(40) So12 PR12	$131,782 to $159,680	11.698 to 11.698	$192,034 to $360,095
Genotype 2 Treatment-Naive cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(70) PR24	$112,767 to $112,767	9.384 to 9.384	-
(3) SOF12 + RBV12	$143,718 to $169,626	10.181 to 10.181	$38,834 to $71,341
Genotype 2 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$104,668 to $104,668	9.600 to 9.600	-
(3) SOF12 + RBV12	$128,116 to $154,162	11.750 to 11.750	$10,906 to $23,020
(40) So12 PR12	$131,511 to $159,409	11.690 to 11.690	$12,843 to $26,192

Table 48: Results of Sensitivity Analysis on Cost of Antiviral Therapy			
Genotype 2 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(3) SOF12 + RBV12	$143,458 to $169,474	9.761 to 9.761	$15,490 to $25,062
(40) So12 PR12	$146,930 to $174,796	10.308 to 10.308	$13,959 to $22,493
(73) SOF16 + RBV16	$159,271 to $195,734	9.896 to 9.896	$20,300 to $33,081
Genotype 3 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,183 to $104,183	9.314 to 9.314	-
(1) PR48	$110,387 to $110,387	11.156 to 11.156	-
(4) SOF24 + RBV24	$172,193 to $227,282	11.734 to 11.734	$106,932 to $202,241
Genotype 3 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$120,843 to $120,843	9.335 to 9.335	-
(4) SOF24 + RBV24	$187,925 to $242,950	10.362 to 10.362	$65,318 to $118,897
Genotype 3 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$103,932 to $103,932	9.167 to 9.167	-
(1) PR48	$112,301 to $112,301	10.879 to 10.879	$4,888 to $4,888
(40) So12 PR12	$134,548 to $163,950	11.510 to 11.510	$13,067 to $25,616
(4) SOF24 + RBV24	$172,667 to $227,982	11.637 to 11.637	$27,828 to $50,222
Genotype 3 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$120,880 to $120,880	8.936 to 8.936	$10,314 to $10,314
(40) So12 PR12	$148,963 to $178,332	10.082 to 10.082	$15,666 to $25,329
(4) SOF24 + RBV24	$187,081 to $242,332	9.661 to 9.661	$32,745 to $53,849
Genotype 4 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$104,904 to $104,904	9.734 to 9.734	-
(1) PR48	$111,496 to $111,496	11.158 to 11.158	-
(4) SOF24 + RBV24	$173,972 to $229,061	11.553 to 11.553	$158,168 to $297,633
Genotype 4 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(1) PR48	$120,087 to $120,087	8.608 to 8.608	-
(4) SOF24 + RBV24	$187,769 to $242,794	10.208 to 10.208	$42,301 to $76,692
Genotype 4 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$104,668 to $104,668	9.596 to 9.596	-
(4) SOF24 + RBV24	$174,106 to $229,421	11.503 to 11.503	$36,412 to $65,418

Table 48: Results of Sensitivity Analysis on Cost of Antiviral Therapy			
Genotype 4 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$101,355 to $101,355	7.043 to 7.043	-
(4) SOF24 + RBV24	$187,516 to $242,768	10.093 to 10.093	$28,250 to $46,365

ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.
[a]Extendedly dominated.

4.3.3 Baseline Age

To measure the impact of age in the model, a broader age range (40 to 60) was used in this sensitivity analysis. Table 49 summarizes the results. The cost-effectiveness results changed significantly. For the genotype 2 and genotype 4 treatment-naive cirrhotic groups, the generated ICUR for the most cost-effective treatments (genotype 2: (3) SOF12 + RBV12 and genotype 4: (4) SOF24 + RBV24) may be less than $50,000 when compared with PR. The main conclusion for other groups remained unchanged.

Table 49: Results of Sensitivity Analysis on Baseline Age			
Genotype 1 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$97,765 to $107,382	8.277 to 10.728	-
(1) PR48	$103,052 to $119,724	8.991 to 12.219	-
(46) B24 PR28-48 RGT	$122,050 to $142,484	9.337 to 12.939	$26,386 to $65,780
(42) Si12 PR24-48 RGT	$123,342 to $144,343	9.398 to 13.037	$24,805 to $60,490
(32) T12 PR24-48 RGT q8	$124,111 to $144,785	9.360 to 12.976	$27,820 to $67,918
(14) PAR/RIT12 + OMB12 + DAS12	$128,531 to $152,271	9.663 to 13.546	$19,201 to $48,434
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$131,127 to $154,950	9.665 to 13.556	$20,999 to $52,265
(40) So12 PR12	$131,942 to $154,483	9.536 to 13.303	$26,651 to $63,779
(41) So12 PR24-48 RGT	$136,992 to $159,002	9.489 to 13.226	$33,704 to $78,871
(6) SOF12 + LDV12	$137,863 to $161,689	9.679 to 13.573	$25,710 to $60,996
(5) SIM12 + SOF12	$164,040 to $186,771	9.574 to 13.364	$53,265 to $115,004
(72) SOF12+ SIM12+RBV12	$168,212 to $190,673	9.542 to 13.306	$59,945 to $128,764
(4) SOF24 + RBV24	$188,410 to $209,588	9.430 to 13.101	$96,779 to $204,702
Genotype 1 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(1) PR48	$113,779 to $122,044	7.443 to 9.526	-
(42) Si12 PR24-48 RGT	$142,449 to $150,687	8.058 to 10.670	$25,061 to $46,635
(32) T12 PR24-48 RGT q8	$147,134 to $155,252	7.824 to 10.242	$46,598 to $87,366
(40) So12 PR12	$154,126 to $162,457	8.369 to 11.242	$23,504 to $43,642
(46) B24 PR28-48 RGT	$154,465 to $162,457	7.122 to 8.929	Dominated
(6) SOF12 + LDV12	$162,677 to $171,060	8.740 to 11.905	$20,550 to $37,809
(5) SIM12 + SOF12	$186,751 to $195,053	8.514 to 11.495	$37,057 to $68,227
(4) SOF24 + RBV24	$208,165 to $216,221	8.111 to 10.770	$75,843 to $140,983

Table 49: Results of Sensitivity Analysis on Baseline Age			
Genotype 1 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$97,557 to $107,256	8.193 to 10.543	-
(1) PR48	$109,113 to $122,478	8.636 to 11.461	-
(42) Si12 PR24-48 RGT	$126,162 to $145,518	9.218 to 12.658	$14,243 to $39,588
(14) PAR/RIT12 + OMB12 + DAS12	$127,944 to $151,920	9.686 to 13.588	$8,853 to $28,040
(39) T12 PR48 q8	$129,137 to $149,816	9.353 to 12.973	$13,243 to $38,128
(68) Si12 PR48	$130,501 to $151,196	9.363 to 12.986	$14,025 to $39,502
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	$130,635 to $154,854	9.703 to 13.632	$9,913 to $30,343
(74) B32 PR36-48 RGT	$130,924 to $149,857	9.177 to 12.604	$19,083 to $50,608
(40) So12 PR12	$136,553 to $158,019	9.420 to 13.060	$17,161 to $45,333
(6) SOF12 + LDV12	$139,747 to $162,985	9.617 to 13.444	$15,448 to $41,292
(72) SOF12+ SIM12+RBV12	$174,842 to $193,419	9.145 to 12.486	$64,125 to $139,374
(5) SIM12 + SOF12	$179,826 to $193,332	8.645 to 11.453	Dominated to $7,872,618
Genotype 1 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(1) PR48	$113,649 to $121,868	6.947 to 8.587	-
(42) Si12 PR24-48 RGT	$142,271 to $150,491	7.900 to 10.376	$15,999 to $30,035
(74) B32 PR36-48 RGT	$147,158 to $155,241	7.510 to 9.654	$31,404 to $59,278
(39) T12 PR48 q8	$147,288 to $155,394	7.707 to 10.019	$23,491 to $44,113
(68) Si12 PR48	$148,555 to $156,641	7.596 to 9.804	$28,681 to $53,579
(40) So12 PR12	$156,064 to $164,252	7.634 to 9.891	$32,527 to $61,695
(10) SOF12 + LDV12 + RBV12	$166,311 to $174,612	8.320 to 11.144	$20,595 to $38,415
(5) SIM12 + SOF12	$186,391 to $194,662	8.345 to 11.183	$28,021 to $52,070
(7) SOF24 + LDV24	$227,806 to $235,826	8.291 to 11.081	$45,772 to $84,790
Genotype 2 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(70) PR24	$86,121 to $107,858	9.453 to 13.148	-
(0) no treatment	$97,765 to $107,382	8.277 to 10.728	-
(3) SOF12 + RBV12	$129,416 to $152,586	9.604 to 13.432	$152,447 to $296,207
(40) So12 PR12	$131,347 to $154,230	9.567 to 13.366	$207,459 to $406,773
Genotype 2 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(70) PR24	$106,211 to $114,557	7.938 to 10.449	-
(3) SOF12 + RBV12	$152,811 to $161,166	8.490 to 11.457	$46,230 to $84,437
Genotype 2 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$97,557 to $107,256	8.190 to 10.540	-
(3) SOF12 + RBV12	$129,423 to $152,717	9.610 to 13.440	$10,988 to $32,015
(40) So12 PR12	$131,079 to $153,972	9.560 to 13.350	$11,930 to $34,099
Genotype 2 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(3) SOF12 + RBV12	$152,717 to $161,017	8.200 to 10.926	$16,834 to $30,491

Table 49: Results of Sensitivity Analysis on Baseline Age			
(40) So12 PR12	$154,103 to $162,473	8.576 to 11.620	$14,325 to $26,089
(73) SOF16 + RBV16	$170,858 to $179,117	8.293 to 11.097	$21,096 to $38,157
Genotype 3 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$97,135 to $106,994	8.022 to 10.167	-
(1) PR48	$97,627 to $117,475	9.205 to 12.649	-
(4) SOF24 + RBV24	$185,156 to $208,220	9.587 to 13.421	$113,379 to $237,552
Genotype 3 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(1) PR48	$114,317 to $122,629	7.902 to 10.388	-
(4) SOF24 + RBV24	$208,729 to $216,865	8.609 to 11.690	$72,513 to $133,290
Genotype 3 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$96,956 to $106,808	7.925 to 9.981	-
(1) PR48	$100,340 to $118,828	9.029 to 12.275	$1,475 to $10,887
(40) So12 PR12	$135,299 to $157,468	9.449 to 13.114	$12,238 to $33,241
(4) SOF24 + RBV24	$186,052 to $208,579	9.528 to 13.287	$26,950 to $63,488
Genotype 3 Treatment-Experienced cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(1) PR48	$114,454 to $122,743	7.633 to 9.878	$8,104 to $14,724
(40) So12 PR12	$156,942 to $165,278	8.421 to 11.334	$16,142 to $29,321
(4) SOF24 + RBV24	$208,169 to $216,226	8.132 to 10.799	$34,376 to $61,793
Genotype 4 Treatment-Naive Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$97,765 to $107,382	8.277 to 10.728	-
(1) PR48	$99,155 to $118,119	9.199 to 12.652	-
(4) SOF24 + RBV24	$187,734 to $209,305	9.467 to 13.176	$169,043 to $340,244
Genotype 4 Treatment-Naive Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. PR**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(1) PR48	$113,739 to $122,000	7.409 to 9.461	-
(4) SOF24 + RBV24	$208,610 to $216,729	8.504 to 11.496	$46,620 to $86,510
Genotype 4 Treatment-Experienced Non-cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$97,557 to $107,256	8.193 to 10.543	-
(4) SOF24 + RBV24	$188,124 to $209,458	9.439 to 13.105	$35,350 to $82,024
Genotype 4 Treatment-Experienced Cirrhotic			
Treatment	**Total Cost**	**Total QALYs**	**ICUR vs. No Treatment**
(0) no treatment	$95,313 to $103,146	6.302 to 7.516	-
(4) SOF24 + RBV24	$208,500 to $216,606	8.428 to 11.347	$29,545 to $53,368

ICUR = incremental cost-utility ratio; PR = pegylated interferon plus ribavirin; QALY = quality-adjusted life-year. Refer to Table 2 for treatment description.

4.3.4 Other Parameters

Several other parameters were also addressed in the deterministic sensitivity analysis, including:

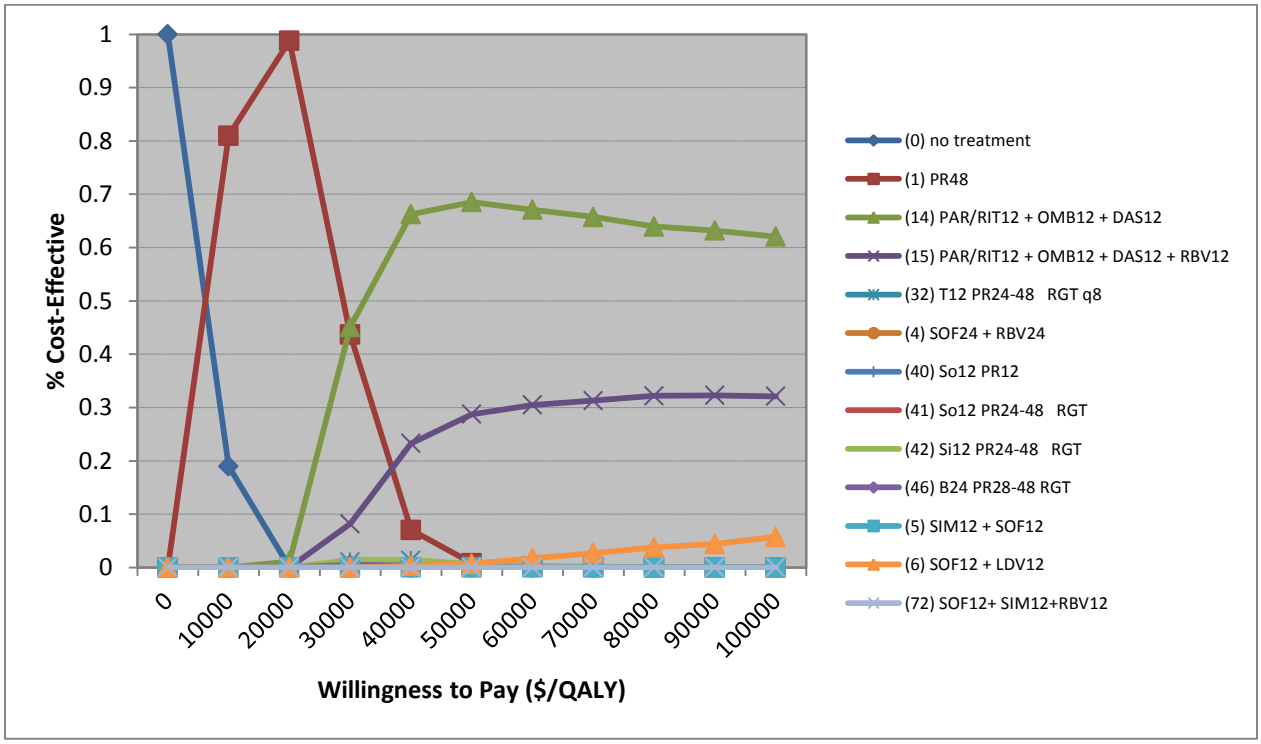
- fibrosis stage distribution
- CHC infection-related costs, utilities, mortality, CHC infection progression
- adverse events (costs, disutility associated with adverse events, relative risk from the NMA)
- discount rate.

Varying the above parameters did not significantly change the base-case analysis results. Results of these sensitivity analyses are presented in Appendix 3.

4.4 Probabilistic Sensitivity Analysis

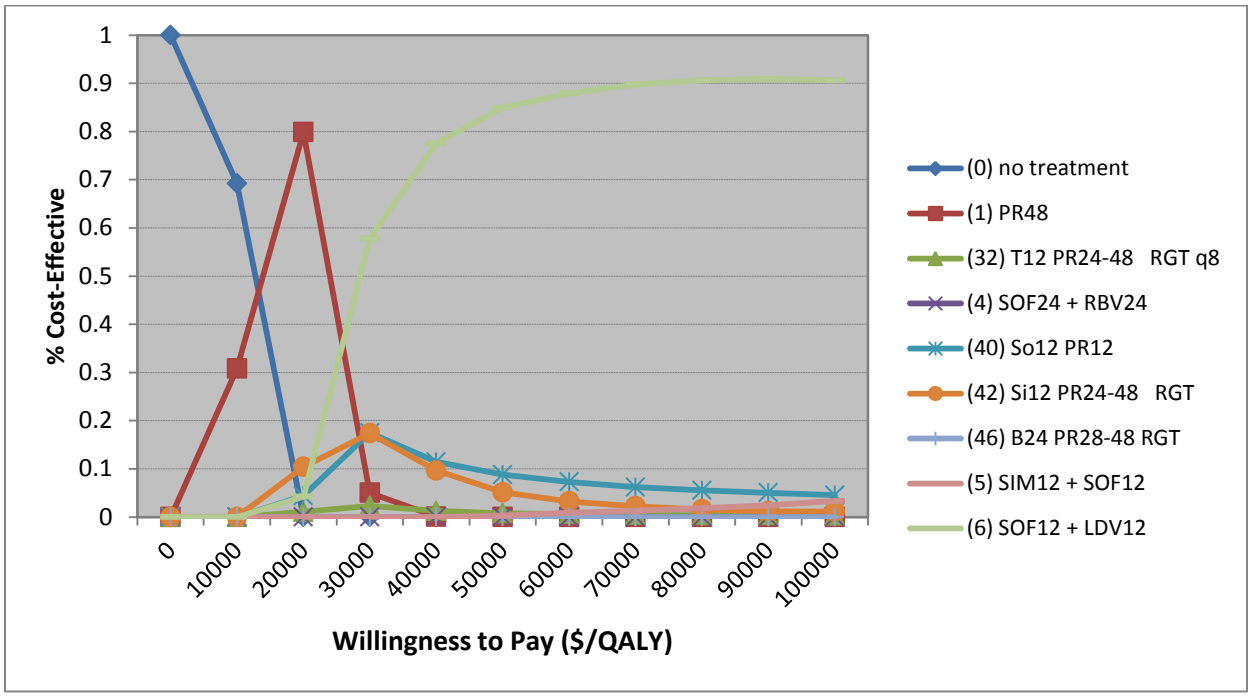
For genotype 1 treatment-naive non-cirrhotic patients, (14) PAR/RIT12 + OMB12 + DAS12 had a 68.5% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold, followed by 28.8% probability for (15) PAR/RIT12 + OMB12 + DAS12 +RBV12, 0.8% for (1) PR48 alone and 0.7% probability for (6) SOF12+LDV12. Figure 2 summarizes the results in a cost-effectiveness acceptability curve.

Figure 2: Cost-Effectiveness Acceptability Curve for Genotype 1 Treatment-Naive Non-Cirrhotic Patients



For genotype 1 treatment-naive patients with cirrhosis, (6) SOF12 + LDV12 had an 85.0% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold, followed by 8.8% probability for (40) So12 PR12, and 5.1% probability for (42) Si12 PR24-48 RGT. Figure 3 summarizes the results in a cost-effectiveness acceptability curve.

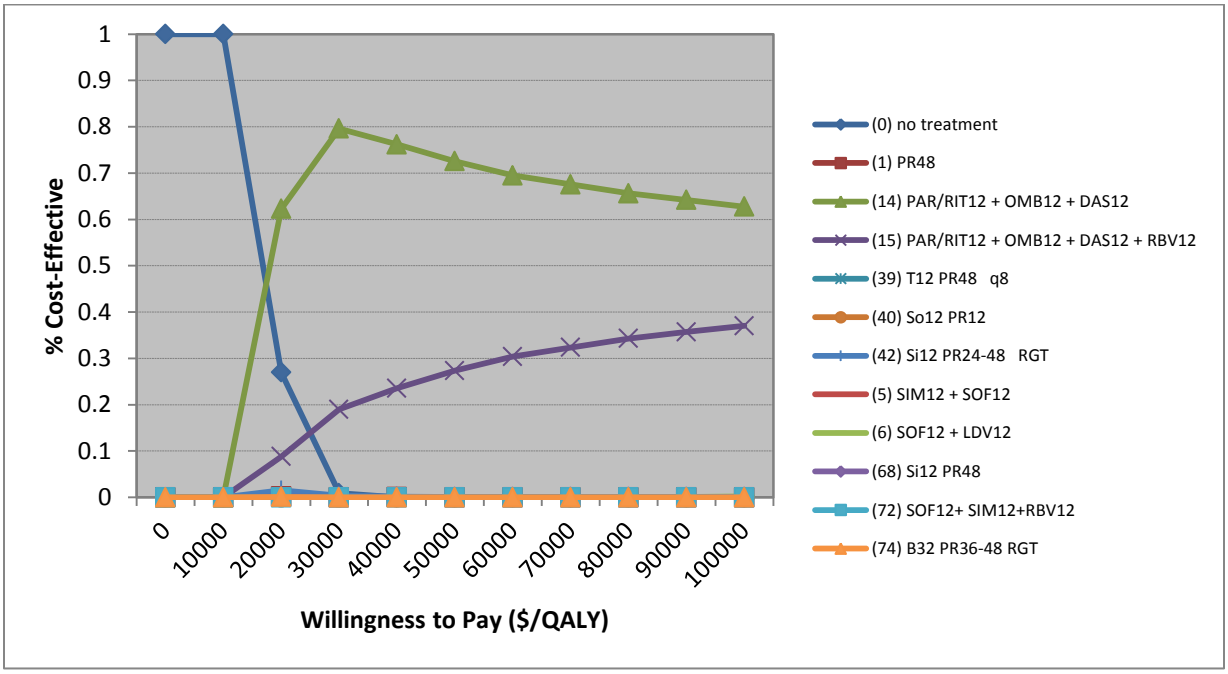
Figure 3: Cost-Effectiveness Acceptability Curve for Genotype 1 Treatment-Naive Cirrhotic Patients



For genotype 1 treatment-experienced non-cirrhotic patients, (14) PAR/RIT12 + OMB12 + DAS12 had a 72.5% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold, followed by 27.4% probability for (15) PAR/RIT12 + OMB12 + DAS12 + RBV12 – Figure 4.

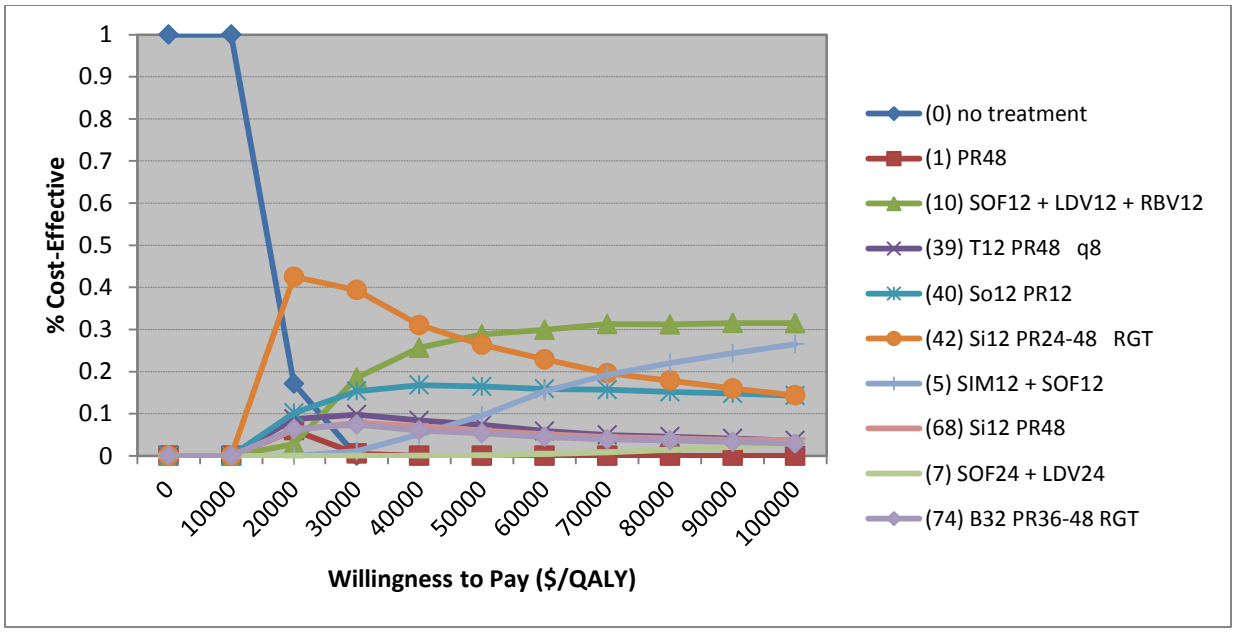
Figure 4 summarizes the results in a cost-effectiveness acceptability curve.

Figure 4: Cost-Effectiveness Acceptability Curve for Genotype 1 Treatment-Experienced Non-cirrhotic Patients



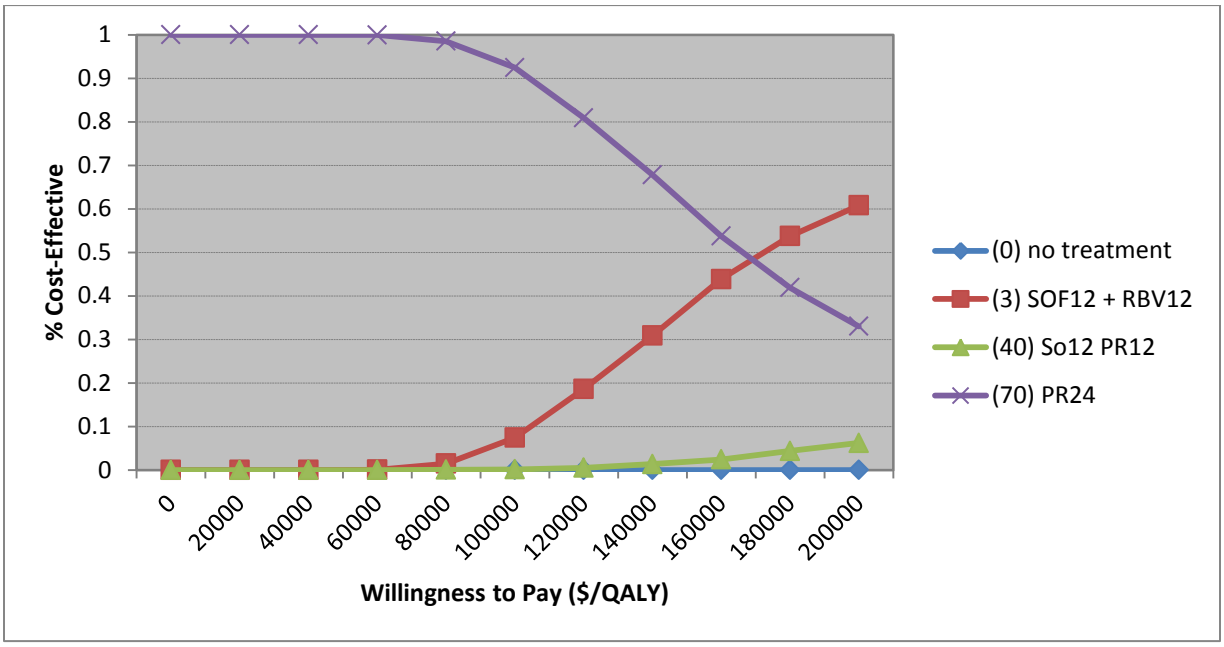
For genotype 1 treatment-experienced patients with cirrhosis, (10) SOF12 + LDV12 + RBV12 had a 28.9% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold, followed by 26.4% probability for (42) Si12 PR24-48 RGT, 16.5% chance for (40) So12 PR12, and 9.6% chance for (5) SIM12 + SOF12. Figure 5 summarizes the results in a cost-effectiveness acceptability curve.

Figure 5: Cost-Effectiveness Acceptability Curve for Genotype 1 Treatment-Experienced Cirrhotic Patients



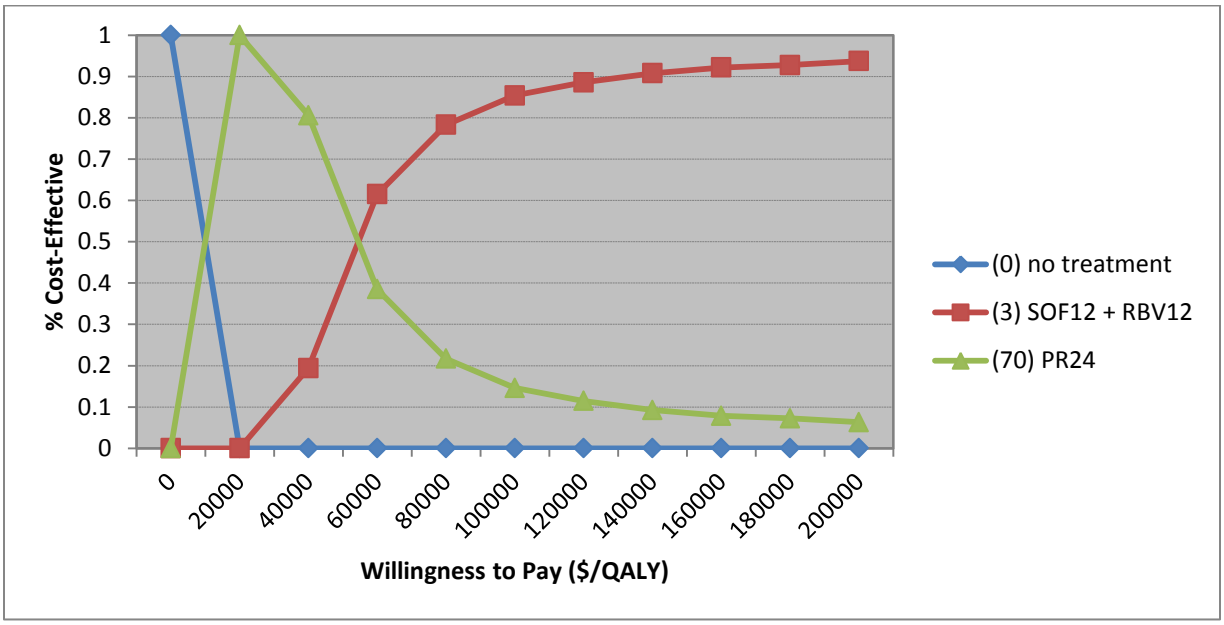
For genotype 2 treatment-naive non-cirrhotic patients, (70) PR24 had a 92.5% probability of being the most cost-effective regimen, using a $100,000 per QALY threshold, followed by 7.5% probability for (3) SOF12 + RBV12. Figure 6 summarizes the results in a cost-effectiveness acceptability curve.

Figure 6: Cost-Effectiveness Acceptability Curve for Genotype 2 Treatment-Naive Non-cirrhotic Patients



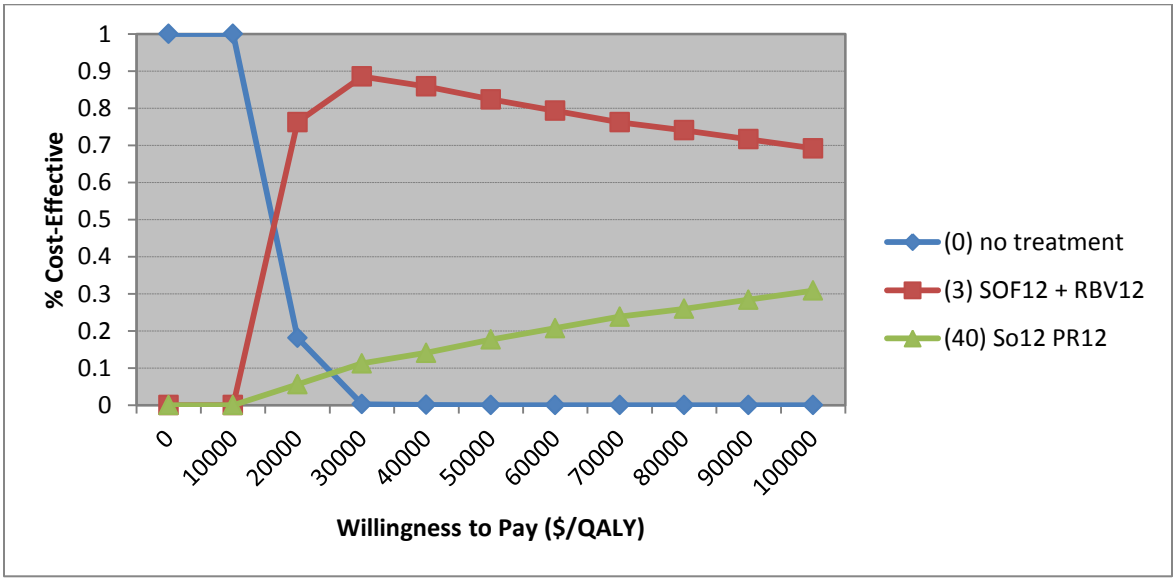
For genotype 2 treatment-naive patients with cirrhosis, (70) PR24 had a 56.5% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold, followed by 43.5% probability for (3) SOF12 + RBV12. Figure 7 summarizes the results in a cost-effectiveness acceptability curve.

Figure 7: Cost-Effectiveness Acceptability Curve for Genotype 2 Treatment-Naive Cirrhotic Patients



For genotype 2 treatment-experienced non-cirrhotic patients, (3) SOF12 + RBV12 had an 82.4% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold, followed by 17.6% probability for (40) So12 PR12. Figure 8 summarizes the results in a cost-effectiveness acceptability curve.

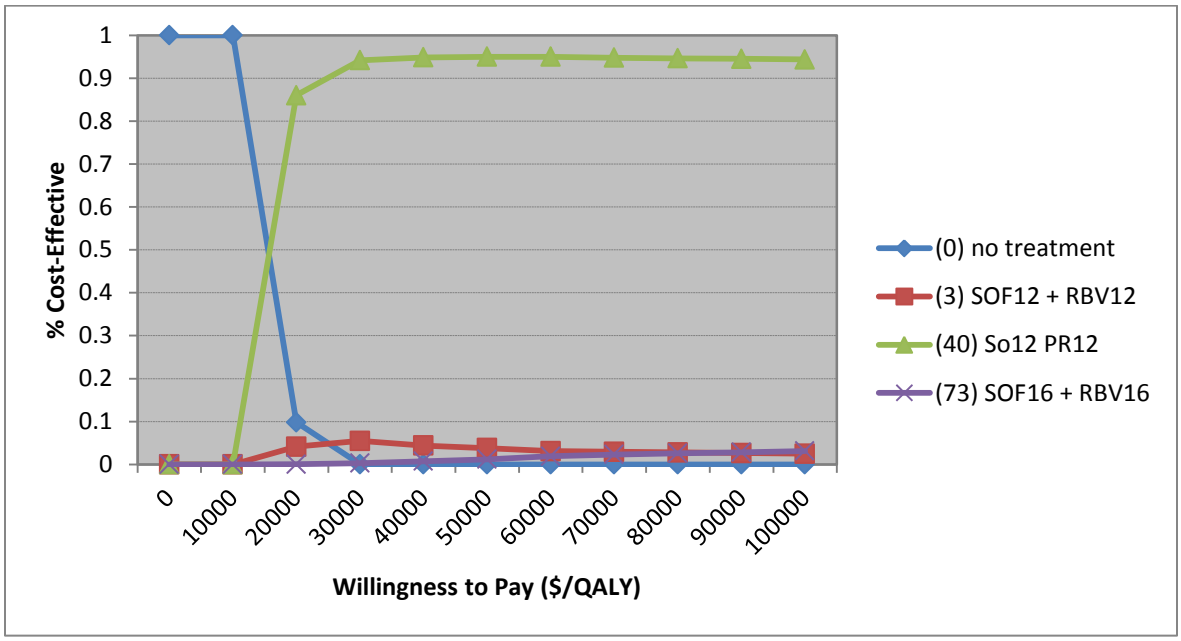
Figure 8: Cost-Effectiveness Acceptability Curve for Genotype 2 Treatment-Experienced Non-cirrhotic Patients



For genotype 2 treatment-experienced patients with cirrhosis, (40) So12 PR12 had a 95.0% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold,

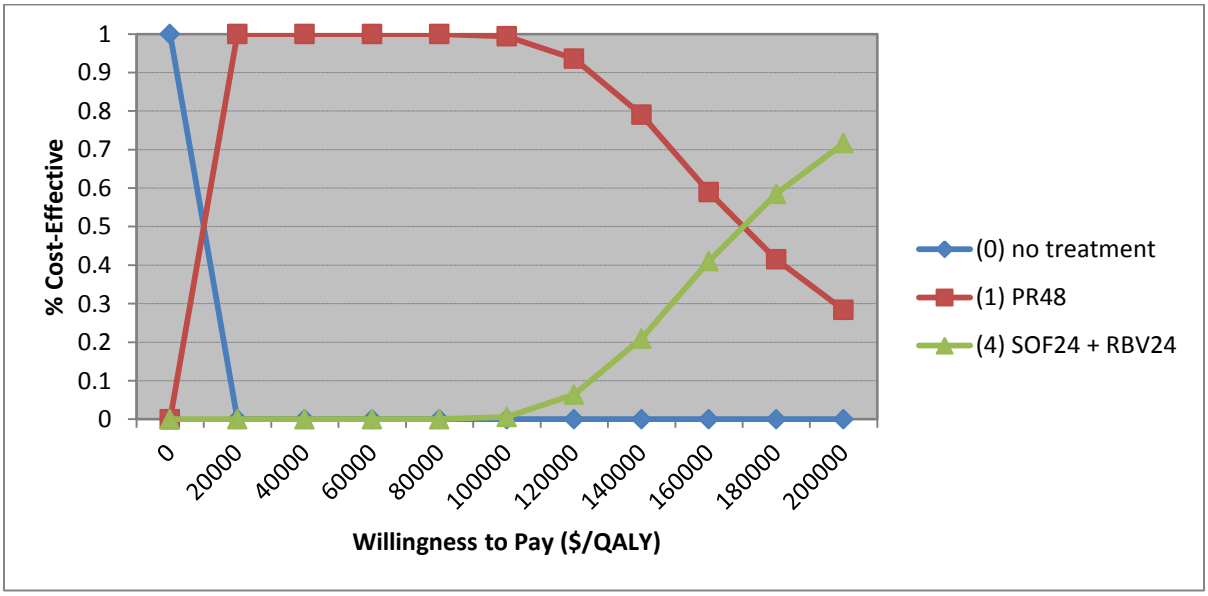
followed by 3.8% probability for (3) SOF12 + RBV12, and 1.2% probability for (73) SOF16 + RBV16. Figure 9 summarizes the results in a cost-effectiveness acceptability curve.

Figure 9: Cost-Effectiveness Acceptability Curve for Genotype 2 Treatment-Experienced Cirrhotic Patients



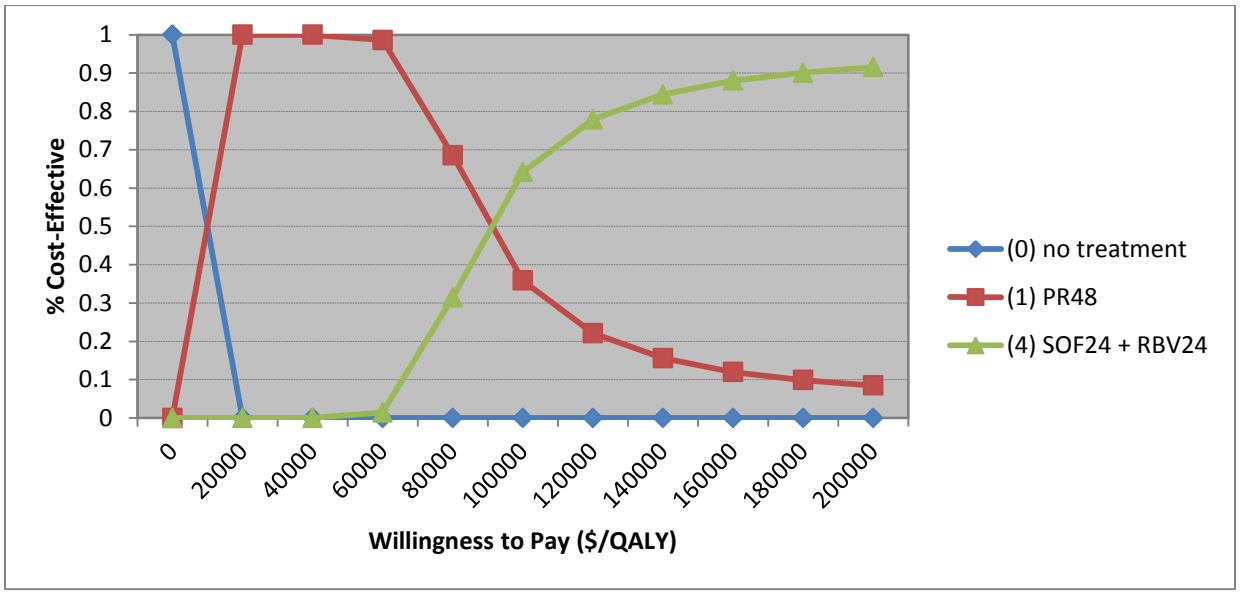
For genotype 3 treatment-naive non-cirrhotic patients, (1) PR48 had a 99.4% probability of being the most cost-effective regimen, using a $100,000 per QALY threshold, followed by 0.6% probability for (4) SOF24 + RBV24. Figure 10 summarizes the results in a cost-effectiveness acceptability curve.

Figure 10: Cost-Effectiveness Acceptability Curve for Genotype 3 Treatment-Naive Non-cirrhotic Patients



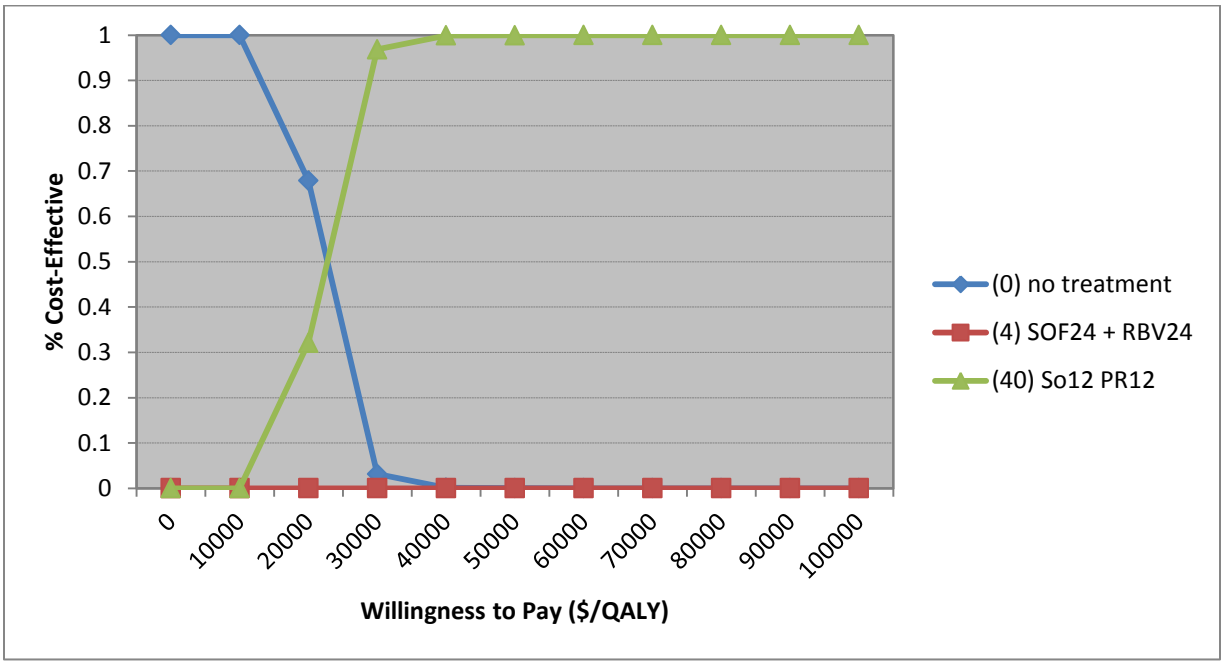
For genotype 3 treatment-naive patients with cirrhosis, (4) SOF24 + RBV24 had a 64.2% probability of being the most cost-effective regimen, using a $100,000 per QALY threshold, followed by 35.8% probability (1) PR48. Figure 11 summarizes the results in a cost-effectiveness acceptability curve.

Figure 11: Cost-Effectiveness Acceptability Curve for Genotype 3 Treatment-Naive Cirrhotic Patients



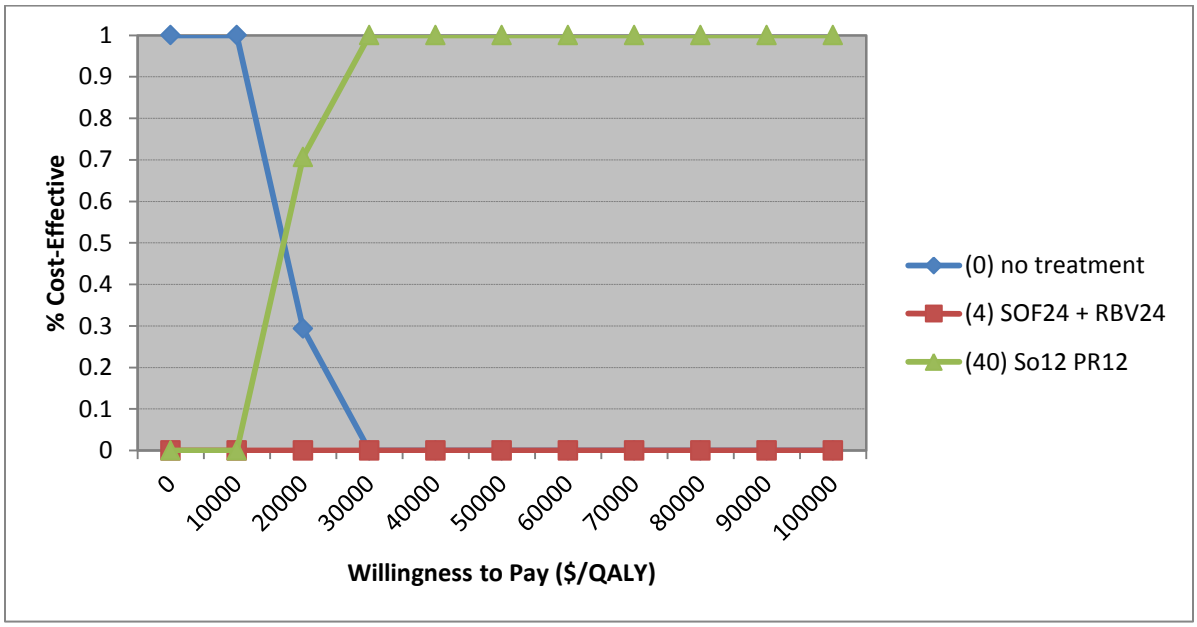
For genotype 3 treatment-experienced non-cirrhotic patients, (40) So12 PR12 had a 99.9% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold, followed by 0.1% probability for (0) no treatment. Figure 12 summarizes the results in a cost-effectiveness acceptability curve.

Figure 12: Cost-Effectiveness Acceptability Curve for Genotype 3 Treatment-Experienced Non-cirrhotic Patients



For genotype 3 treatment-experienced patients with cirrhosis, (40) So12 PR12 had a 100% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold. Figure 13 summarizes the results in a cost-effectiveness acceptability curve.

Figure 13: Cost-Effectiveness Acceptability Curve for Genotype 3 Treatment-Experienced Cirrhotic Patients



For genotype 4:

- treatment-naive non-cirrhotic patients. (1) PR48 had a 92.6% probability of being the most cost-effective regimen, using a $50,000 per QALY threshold
- treatment-naive patients with cirrhosis, (1) PR48 had a 53.7% probability of being the most cost-effective agent, using a $50,000 per QALY threshold, followed by 24.9% probability for (4) SOF24 + RBV24

5 DISCUSSION

The results of the base-case analysis suggest that for each genotype 1 population (treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic or treatment-experienced cirrhotic), at least one of the interferon-free therapies appears to be economically attractive compared with PR alone. The drug that is the most cost-effective varies by population, but was generally consistent across fibrosis stages.

For patients with **genotype 1** CHC infection who are **treatment-naive** and non-cirrhotic, at a willingness to pay (λ) of $50,000 per QALY, PAR/RIT12 + OMB12 + DAS12 is likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-naive and cirrhotic, SOF12 + LDV12 is likely to be the most cost-effective option compared with PR alone. The analysis also suggests that for patients with genotype 1 CHC infection who are **treatment-experienced** and non-cirrhotic: at a willingness to pay of $50,000 per QALY, PAR/RIT12 + OMB12 + DAS12 is likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-experienced and cirrhotic, Si12 PR24-48 RGT is likely to be the most cost-effective option followed by SOF12 + LDV12 + RBV12 compared with PR alone.

The results of the base-case analysis suggest that for each **genotype 2, genotype 3, and genotype 4** treatment naive population (non-cirrhotic and cirrhotic), the interferon-free or the PR-based DAAs therapies appear not to be economically attractive compared with PR alone. At a willingness to pay of $50,000 per QALY, PR alone is still the most cost-effective for these populations and is generally consistent across fibrosis stages.

The analysis also suggests that for each genotype 2, genotype 3, and genotype 4 treatment-experienced population (non-cirrhotic and cirrhotic), there are interferon-free or the PR-based DAAs therapies that appear to be attractive at a willingness to pay of $50,000 per QALY when compared with no treatment.

For patients with **genotype 2** CHC infection who are treatment-experienced and non-cirrhotic, SOF12 + RBV12 is likely to be the most cost-effective option. For patients with genotype 2 CHC infection who are treatment-experienced and cirrhotic, So12 PR12 is likely to be the most cost-effective option**.** For patients with **genotype 3** CHC infection who are treatment-experienced and non-cirrhotic, So12 PR12 is likely to be the most cost-effective option. For patients with genotype 3 CHC infection who are treatment-experienced and cirrhotic, So12 PR12 is likely to be the most cost-effective option. Lastly, for patients with **genotype 4** CHC infection who are treatment-experienced SOF24 + RBV24 is likely to be the most cost-effective option.

In the analyses that were stratified by fibrosis stage, ICURs for the interferon-free regimens compared with PR alone tended to be lower (more cost-effective) in patients with advanced fibrosis (F3) compared with patients with no or mild fibrosis (F0 to F2).

Extensive sensitivity analyses were conducted around the model input parameters, and the structural uncertainty was tested. Besides treatment efficacy, the main factors affecting the cost-effectiveness of the new interferon-free or the PR-based DAAs regimens versus PR alone were baseline age and the cost of antiviral therapies. The analyses showed that ICURs of new interferon-free or the PR-based DAAs therapies compared with PR tended to be lower (i.e., new interferon-free or the PR-based DAAs are more cost-effective) in younger patients. Additionally,

the sensitivity analyses also showed that the cost-effectiveness results are highly sensitive to drug acquisition costs.

Results of both the multiple one-way sensitivity analyses and PSA provide evidence that PAR/RIT12 + OMB12 + DAS12 is likely to remain cost-effective despite the uncertainty in the model's parameters for genotype 1 treatment-naive non-cirrhotic patients; SOF12 + LDV12 is likely to remain cost-effective for genotype 1 treatment-naive patients with cirrhosis; PAR/RIT12 + OMB12 + DAS12 is likely to remain cost-effective for genotype 1 treatment-experienced non-cirrhotic patients. However, due to the wide confidence intervals in the efficacy data for genotype 1 treatment-experienced patients with cirrhosis, the conclusions are uncertain.

The sensitivity analyses also suggested that PR is likely to remain the most cost-effective at a willingness to pay threshold of $50,000 per QALY for genotype 2, genotype 3, and genotype 4 treatment naive populations (non-cirrhotic and cirrhotic). For genotype 2 treatment-experienced non-cirrhotic patients, SOF12 + RBV12 is likely to remain cost-effective when compared with no treatment; for genotype 2 treatment-experienced patients with cirrhosis, So12 PR12 RBV12 is likely to remain cost-effective when compared with no treatment. For genotype 3 treatment-experienced patients (non-cirrhotic and cirrhotic), So12 PR12 is likely to remain cost-effective when compared with no treatment. Of note, So12 PR12 is an indicated treatment for genotype 4 infection that could not be assessed for cost effectiveness due to the lack of efficacy data by cirrhosis status.

5.1 Strength and Limitations

5.1.1 Strengths

The economic model used best available utility data as well as costing data, which were also grounded on Canadian data. Sensitivity analysis showed that the results remained consistent when other utility sources were used. The model also used the best available fibrosis progression data from the literature, and it was validated against other existing models. Furthermore, the model used efficacy data stratified by genotype, treatment status, cirrhosis status, which allowed for assessment of the cost-effectiveness of regimens in these specific populations.

5.1.2 Key Limitations

As with all economic models, a number of assumptions were made in this economic evaluation. First, comparative efficacy was based on findings for cirrhotic versus non-cirrhotic from the NMA. Ideally, the NMA should have been stratified by individual fibrosis stages. Patients with a fibrosis stage F3 should have been analyzed separately from F0 to F2. This was not possible because the sample sizes were very small, and sometimes studies only reported data grouped by F0 to F3.

Because no NMA stratified by fibrosis stage could be performed due to insufficient reporting in the clinical trials, the assumption was made that the incidence of adverse events is not affected by cirrhosis status or genotype. Furthermore, there were very few data available in the literature on the disutility associated with adverse events. Adverse events were not shown to have a big impact on the results. Sensitivity analyses in which no disutility was applied were not substantively different from the base case. Costs associated with adverse events contributed to less than 1% of total costs, for all treatments and populations.

The CHC infection progression parameters used by the model were derived from published studies conducted in various countries. While these parameters may not exactly reflect the Canadian population, they are likely to be reasonably representative. Although there is likely some uncertainty regarding the true transition rates, these rates are the most robust currently available in the literature and were acceptable to the clinical experts. The CHC infection-related costs used were not fibrosis stage-specific; they may overestimate the cost of mild/no fibrosis and underestimate the cost of severe fibrosis. The utilities of CHC infected patients who have late-stage liver disease (decompensated cirrhosis and HCC) used in the model were based on very small sample sizes and may not cover the full spectrum of the severity of the disease.

The economic analyses do not account for any confidential prices that have been negotiated for CHC infection therapies.

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APPENDIX 1: ALTERNATIVE UTILITIES INPUTS USED FOR SENSITIVITY ANALYSIS

Table 50: CHC infection-Related Utilities Used in Sensitivity Analysis	
Description	**Base Estimate**
Utility for CHC infection-Related Health States	
Non-cirrhosis	0.79
Compensated cirrhosis	0.80
HCC	0.75
Decompensated cirrhosis	0.60
Post-transplant	0.73
Non-cirrhosis on treatment (apply only to regimens contains PEG or RBV)	0.77
Non-cirrhosis viral clearance	0.86
Compensated cirrhosis on treatment (apply only to regimens contains PEG or RBV)	0.78
Compensated cirrhosis viral clearance	0.87

CHC = chronic hepatitis C; HCC = Hepatocellular carcinoma.

APPENDIX 2: EFFICACY AND ADVERSE EVENTS DATA INPUTS USED FOR THE EXPLORATORY ECONOMIC ANALYSES

Table 51: Treatment Efficacy (Sustained Virologic Response) Including DAC24 + ASU24 and DAC12 + SOF12				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Note**
Genotype 1 Treatment-Naive				
Non-cirrhosis				
Reference baseline (1) PR48	0.4913[a]	0.4359	0.5456	Based on NMA
(17) DAC24 + ASU24	1.819	1.637	2.028	Based on NMA
(19) DAC12 + SOF12	1.898	1.276	2.212	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.3958[a]	0.3092	0.4906	Based on NMA
(17) DAC24 + ASU24	2.253	1.657	2.956	Based on NMA
Genotype 1 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (1) PR48	0.2571[a]	0.2242	0.292	Based on NMA
(17) DAC24 + ASU24	3.073	2.417	3.693	Based on NMA
(18) DAC24 + ASU24 + PR24	3.372	2.56	3.966	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.1691[a]	0.1165	0.2334	Based on NMA
(17) DAC24 + ASU24	5.058	3.118	7.648	Based on NMA
(18) DAC24 + ASU24 + PR24	5.346	3.729	7.798	Based on NMA
Genotype 3 Treatment-Naive				
Non-cirrhosis				
Reference baseline (1) PR48	0.7051[a]	0.6393	0.765	Based on NMA
(19) DAC12 + SOF12	1.375	1.233	1.525	Based on NMA
Genotype 3 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (1) PR48	0.6082[a]	0.5786	0.6374	Based on NMA
(19) DAC12 + SOF12	1.544	1.306	1.667	Based on NMA
Genotype 4 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (3) SOF12 + RBV12	0.6345[a]	0.4483	0.7983	Based on NMA
(18) DAC24 + ASU24 + PR24	1.485	1.119	2.12	Based on NMA
Cirrhosis				
Reference baseline (3) SOF12 + RBV12	0.5628[a]	0.2422	0.8484	Based on NMA
(18) DAC24 + ASU24 + PR24	1.631	0.9999	3.805	Based on NMA

[a] Baseline probability. RR = relative risk; DAC24 + ASU24: daclatasvir and asunaprevir for 24 weeks; DAC24 + ASU24 + PR24: daclatasvir, asunaprevir and pegylated interferon plus ribavirin for 24 weeks; DAC12 + SOF12: daclatasvir and sofosbuvir for 12 weeks. Refer to Table 2 for other treatment description.

Table 52: Adverse Events including DAC24 + ASU24 and DAC12 + SOF12				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Note**
Treatment-Naive				
Depression				
Reference baseline (1) PR48	0.1381[a]	0.11	0.1683	Based on NMA
(17) DAC24 + ASU24	0.2522	0.07117	0.9184	Based on NMA
(19) DAC12 + SOF12	0.5062	0.03573	3.145	Based on NMA
Anemia				
Reference baseline (1) PR48	0.2136[a]	0.1838	0.2459	Based on NMA
(17) DAC24 + ASU24	0.05568	0.02193	0.1322	Assume same as (6)
(19) DAC12 + SOF12	0.08548	0.005052	0.6961	Based on NMA
Rash				
Reference baseline (1) PR48	0.1828[a]	0.1465	0.2186	Based on NMA
(17) DAC24 + ASU24	0.1307	0.04775	0.3228	Based on NMA
(19) DAC12 + SOF12	0.372	0.05255	1.613	Based on NMA
Treatment-Experienced				
Depression				
Reference baseline (1) PR48	0.1318[a]	0.09864	0.1697	Based on NMA
(17) DAC24 + ASU24	0.1113	0.02161	0.4955	Based on NMA
(18) DAC24 + ASU24 + PR24	0.1113	0.02161	0.4955	Assume same as (18)
Anemia				
Reference baseline (1) PR48	0.1901[a]	0.1625	0.2202	Based on NMA
(17) DAC24 + ASU24	0.275	0.09609	0.7876	Assume same as (18)
(18) DAC24 + ASU24 + PR24	0.275	0.09609	0.7876	Based on NMA
Rash				
Reference baseline (1) PR48	0.1322[a]	0.1071	0.1594	Based on NMA
(17) DAC24 + ASU24	0.2687	0.06724	0.8801	Based on NMA
(18) DAC24 + ASU24 + PR24	2.615	0.9938	4.943	Based on NMA

[a] Baseline probability. RR = relative risk; DAC24 + ASU24: daclatasvir and asunaprevir for 24 weeks; DAC24 + ASU24 + PR24: daclatasvir, asunaprevir and pegylated interferon plus ribavirin for 24 weeks; DAC12 + SOF12: daclatasvir and sofosbuvir for 12 weeks. Refer to Table 2 for other treatment description.

Table 53: Discontinuation Rate including DAC24 + ASU24 and DAC12 + SOF12				
Description	**Base Estimate**	**Lower Limit (95% CI)**	**Upper Limit (95% CI)**	**Note**
Treatment-Naive				
(17) DAC24 + ASU24	0.005	0.001	0.034	
(19) DAC12 + SOF12	0.044	0.023	0.083	Assume same as (6)
Treatment-Experienced				
(17) DAC24 + ASU24	0.002	0.000	0.038	
(18) DAC24 + ASU24 + PR24	0.004	0.001	0.022	

DAC24 + ASU24: daclatasvir and asunaprevir for 24 weeks; DAC24 + ASU24 + PR24: daclatasvir, asunaprevir and pegylated interferon plus ribavirin for 24 weeks; DAC12 + SOF12: daclatasvir and sofosbuvir for 12 weeks.

Table 54: Treatment Efficacy (Sustained Virologic Response) Including SOF8+LDV8 in Genotype 1 Non-cirrhotic Patients				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Note**
Genotype 1 Treatment-Naive				
Non-cirrhosis				
Reference baseline (1) PR48	0.4929[a]	0.437	0.5467	Based on NMA
(4) SOF24 + RBV24	1.624	1.271	1.881	Based on NMA
(5) SIM12 + SOF12	1.73	0.7072	2.163	Based on NMA
(6) SOF12 + LDV12	1.967	1.76	2.217	Based on NMA
(8) SOF8 + LDV8	1.925	1.661	2.188	Based on NMA
(14) PAR/RIT12 + OMB12 + DAS12	1.923	1.245	2.217	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	1.936	1.745	2.176	Based on NMA
(32) T12 PR24-48 RGT q8	1.548	1.302	1.753	Based on NMA
(40) So12 PR12	1.736	1.181	2.038	Based on NMA
(41) So12 PR24-48 RGT	1.728	1.265	2.054	Based on NMA
(42) Si12 PR24-48 RGT	1.588	1.406	1.777	Based on NMA
(46) B24 PR28-48 RGT	1.538	1.267	1.766	Based on NMA
(72) SOF12+ SIM12+RBV12	1.73	0.7072	2.163	Based on NMA

[a] Baseline probability. RR = relative risk; Refer to Table 2 for treatment description.

Table 55: Treatment Efficacy (Sustained Virologic Response) Including PAR/RIT12 + OMB12 + DAS12 + RBV12 in Genotype 1 Cirrhotic Patients				
Description	**Baseline[a] / RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Note**
Genotype 1 Treatment-Naive				
Cirrhosis				
Reference baseline (1) PR48	0.3898[a]	0.3099	0.475	Based on NMA
(4) SOF24 + RBV24	1.76	0.6621	2.592	Based on NMA
(5) SIM12 + SOF12	2.217	1.081	2.937	Based on NMA
(6) SOF12 + LDV12	2.442	1.956	3.091	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	2.416	1.942	3.057	
(32) T12 PR24-48 RGT q8	1.438	0.7411	2.208	Based on NMA
(40) So12 PR12	2.086	1.283	2.777	Based on NMA
(42) Si12 PR24-48 RGT	1.69	1.081	2.403	Based on NMA
(46) B24 PR28-48 RGT	0.6603	0.1573	1.633	Based on NMA
Genotype 1 Treatment-Experienced				
Cirrhosis				
Reference baseline (1) PR48	0.1634 [a]	0.1133	0.2215	Based on NMA

Table 55: Treatment Efficacy (Sustained Virologic Response) Including PAR/RIT12 + OMB12 + DAS12 + RBV12 in Genotype 1 Cirrhotic Patients				
(5) SIM12 + SOF12	4.841	1.905	7.637	Based on NMA
(7) SOF24 + LDV24	4.697	1.63	7.446	Based on NMA
(10) SOF12 + LDV12 + RBV12	4.829	3.094	7.293	Based on NMA
(15) PAR/RIT12 + OMB12 + DAS12 + RBV12	5.491	3.861	7.991	
(39) T12 PR48 q8	3.054	1.37	5.604	Based on NMA
(40) So12 PR12	2.981	0.3428	6.668	Based on NMA
(42) Si12 PR24-48 RGT	3.594	1.517	6.036	Based on NMA
(68) Si12 PR48	2.719	0.8508	5.463	Based on NMA
(74) B32 PR36-48 RGT	2.605	0.6858	6.004	Based on NMA

[a] Baseline probability. RR = relative risk; Refer to Table 2 for treatment description.

Table 56: Treatment Efficacy (Sustained Virologic Response) Including Boson Study for So12+PR12 in Genotype 3 Patients				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Note**
Genotype 3 Treatment-Naive				
Non-cirrhosis				
Reference baseline (1) PR48	0.7064[a]	0.6415	0.7659	Based on NMA
(4) SOF24 + RBV24	1.313	1.166	1.46	Based on NMA
(40) So12 PR12	1.362	1.175	1.513	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.6027[a]	0.5598	0.6447	Based on NMA
(4) SOF24 + RBV24	1.473	1.085	1.679	Based on NMA
(40) So12 PR12	1.559	1.036	1.728	Based on NMA
Genotype 3 Treatment-Experienced				
Non-cirrhosis				
Reference baseline (1) PR48	0.6082[a]	0.5792	0.6374	Based on NMA
(4) SOF24 + RBV24	1.444	1.289	1.567	Based on NMA
(40) So12 PR12	1.54	1.327	1.653	Based on NMA
Cirrhosis				
Reference baseline (1) PR48	0.4773[a]	0.4378	0.5162	Based on NMA
(4) SOF24 + RBV24	1.469	1.185	1.77	Based on NMA
(40) So12 PR12	1.724	1.281	2.021	Based on NMA

[a] Baseline probability. RR = relative risk; Refer to Table 2 for treatment description.

APPENDIX 3: TORNADO DIAGRAMS FOR DETERMINISTIC SENSITIVITY ANALYSES

Figure 14: Tornado Diagram: (14) PAR/RIT12 + OMB12 + DAS12 Versus PR for Genotype 1 Treatment-Naive Non-cirrhotic Patients (ICUR $29,354/QALY)

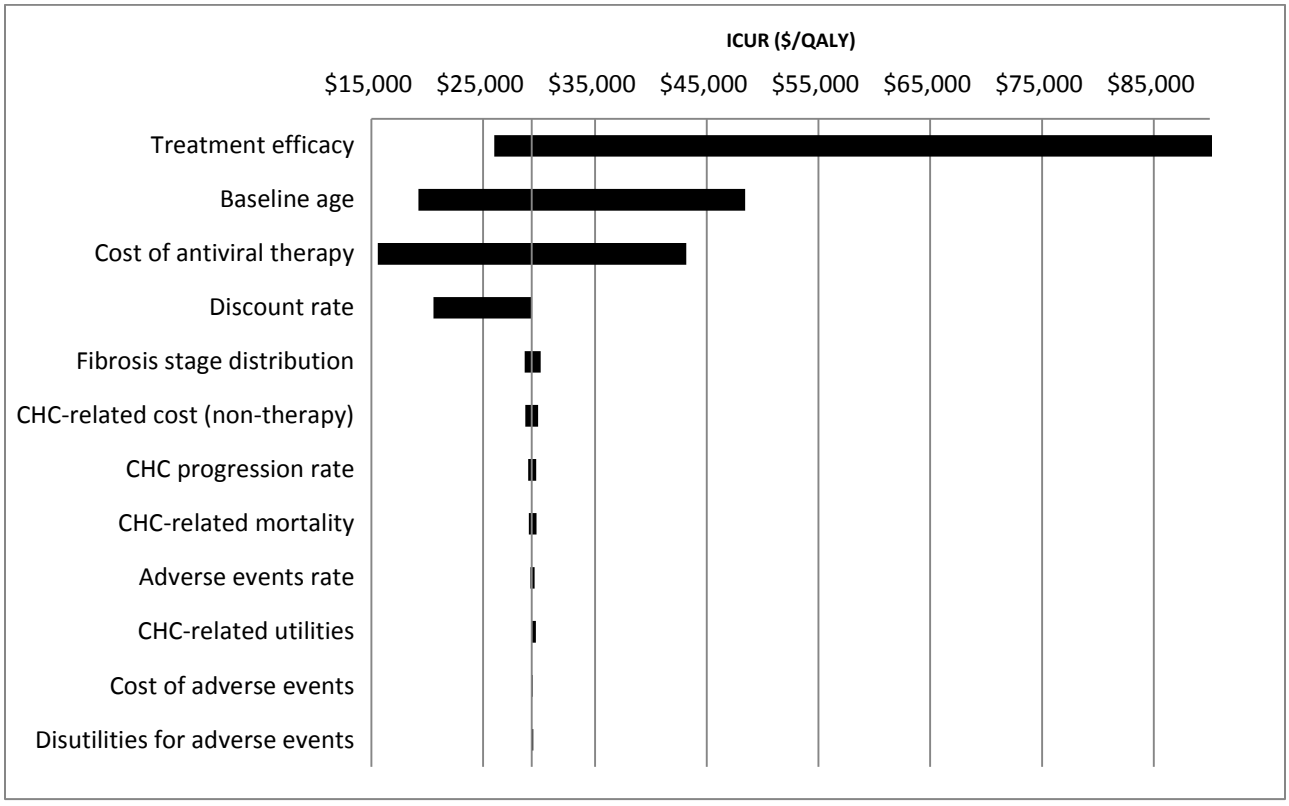

Figure 15: Tornado Diagram: (6) SOF12+LDV12 Versus PR for Genotype 1 Treatment-Naive cirrhotic Patients (ICUR $ 26,261/QALY)

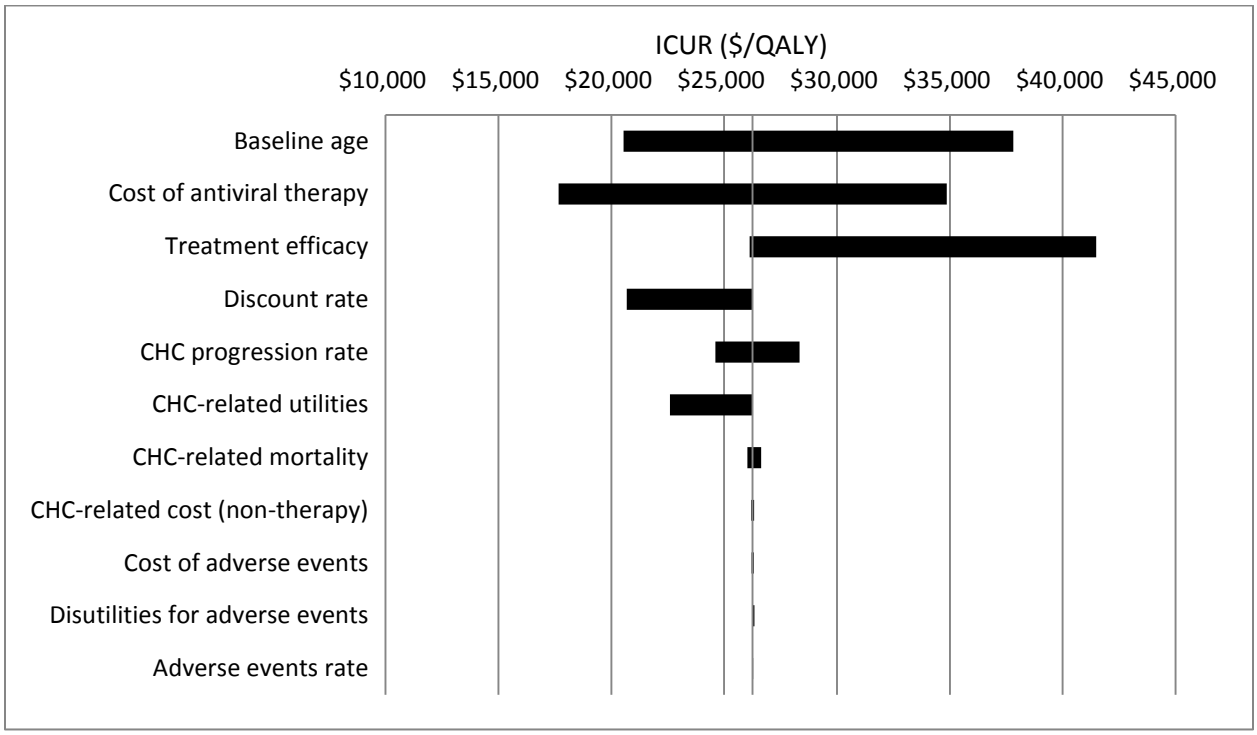

Figure 16: Tornado Diagram: (14) PAR/RIT12 + OMB12 + DAS12 Versus PR for Genotype 1 Treatment-Experienced Non-cirrhotic Patients (ICUR $ 15,506/QALY)

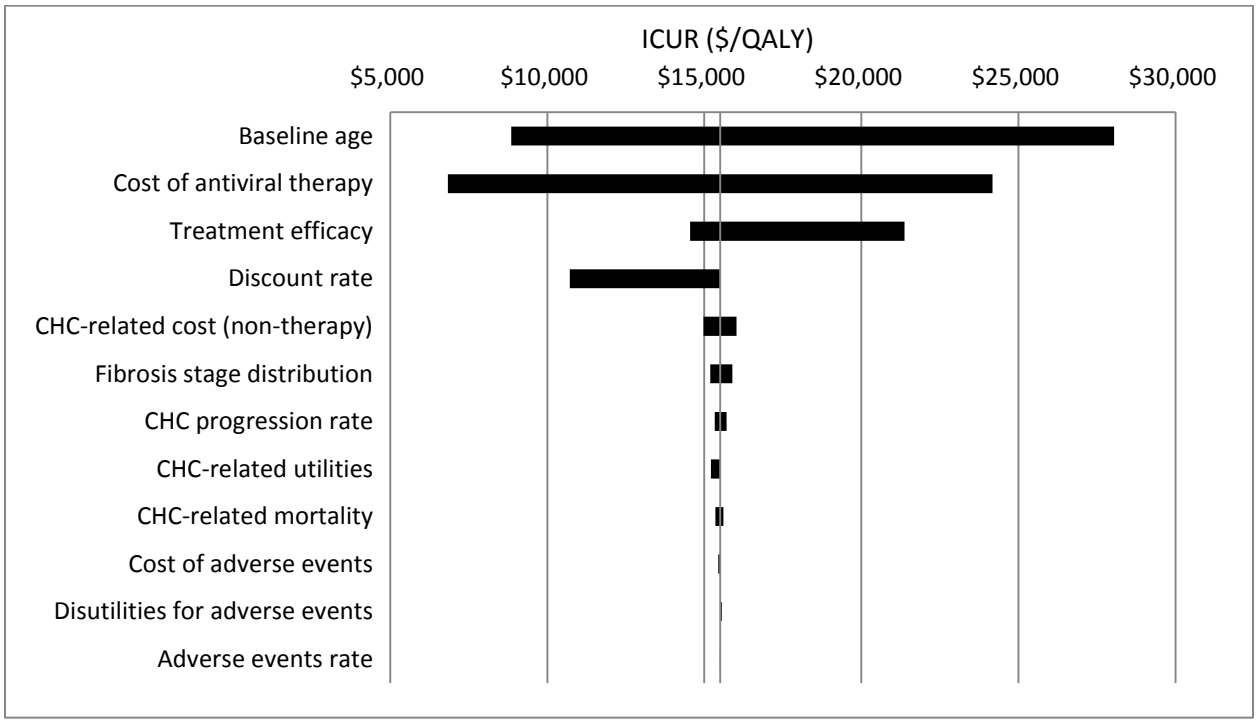

Figure 17: Tornado Diagram: (42) Si12 PR24-48 RGT Versus PR for Genotype 1 Treatment-Experienced Cirrhotic Patients (ICUR $ 20,655/QALY)

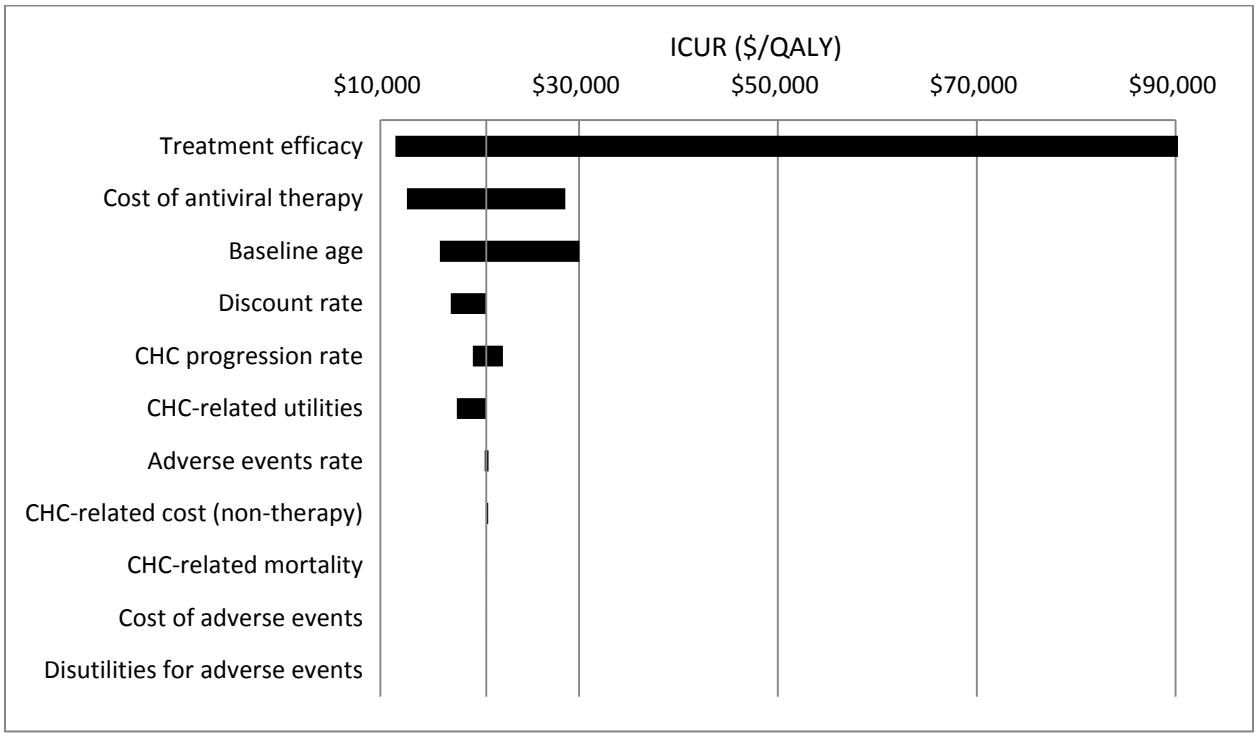

Figure 18: Tornado Diagram: (3) SOF12 + RBV12 Versus PR for Genotype 2 Treatment-Naive Non-cirrhotic Patients (ICUR $ 203,282 /QALY)

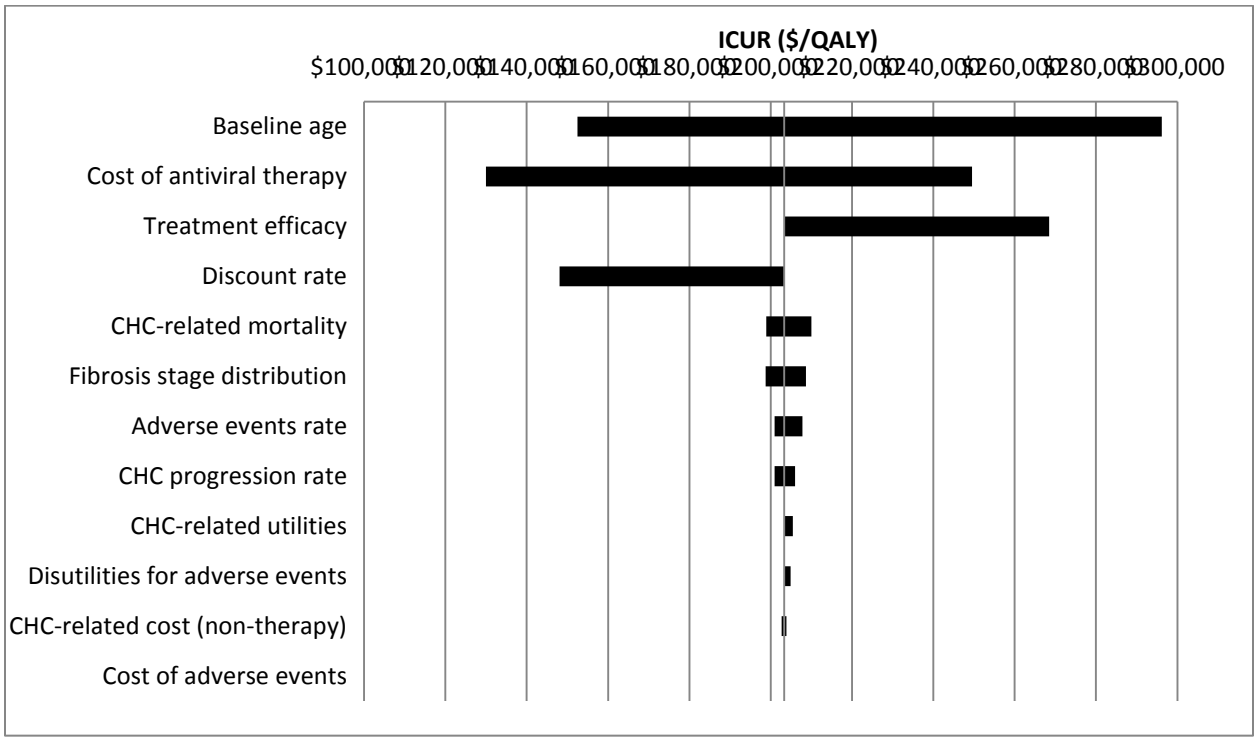

Figure 19: Tornado Diagram: (3) SOF12 + RBV12 Versus PR for Genotype 2 Treatment-Naive Cirrhotic Patients (ICUR $ 58,659 /QALY)

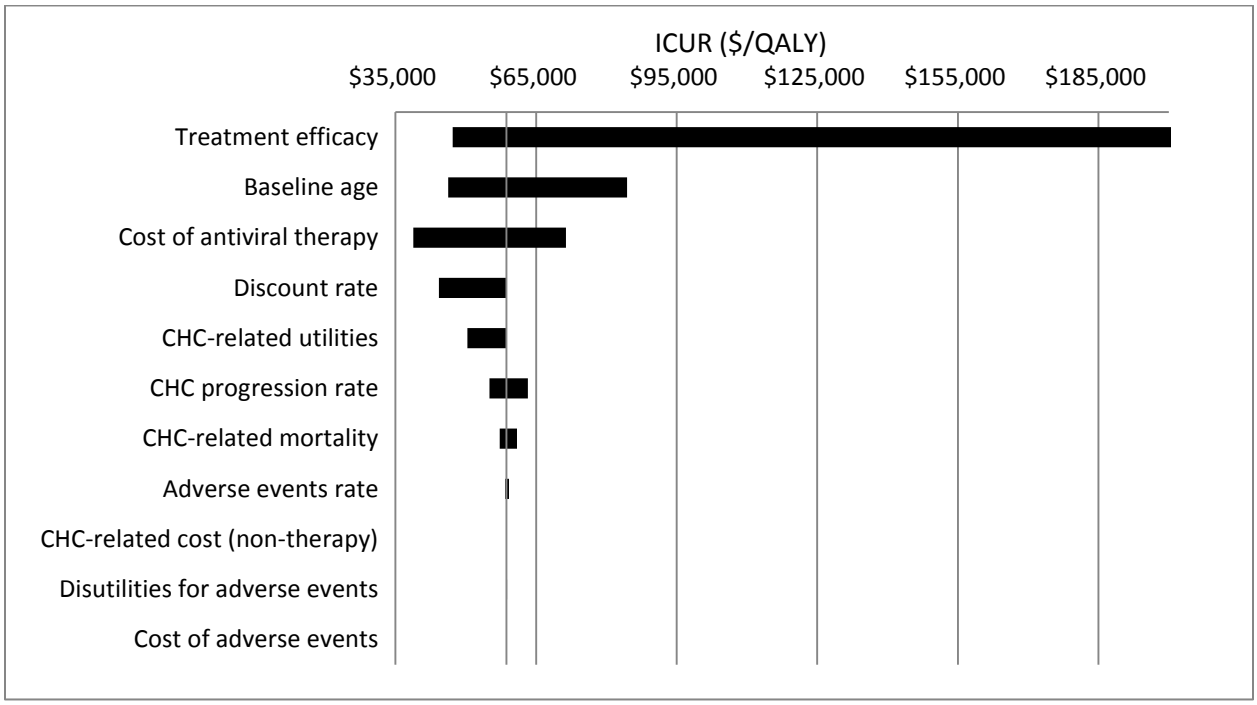

Figure 20: Tornado Diagram: (3) SOF12 + RBV12 Versus No Treatment for Genotype 2 Treatment-Experienced Non-cirrhotic Patients (ICUR $ 18,247 /QALY)

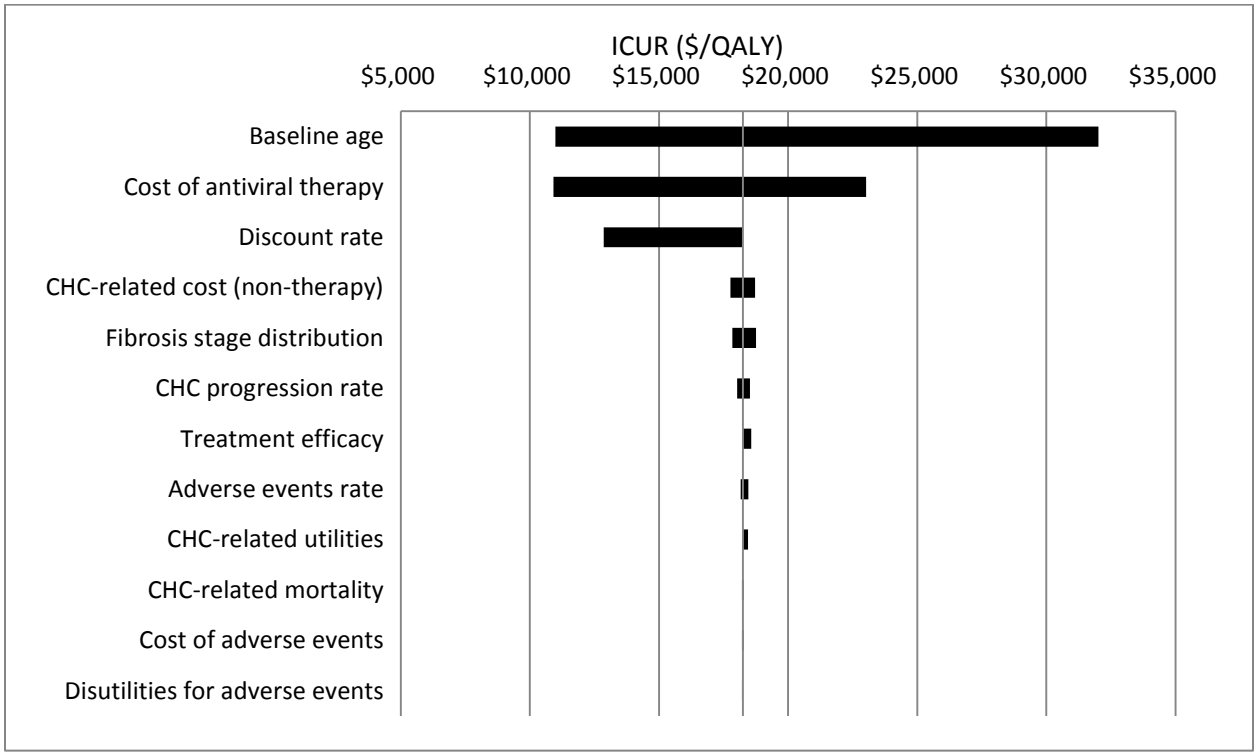

Figure 21: Tornado Diagram: (40) So12 PR12 Versus No Treatment for Genotype 2 Treatment-Experienced Cirrhotic Patients (ICUR $ 18,226 /QALY)

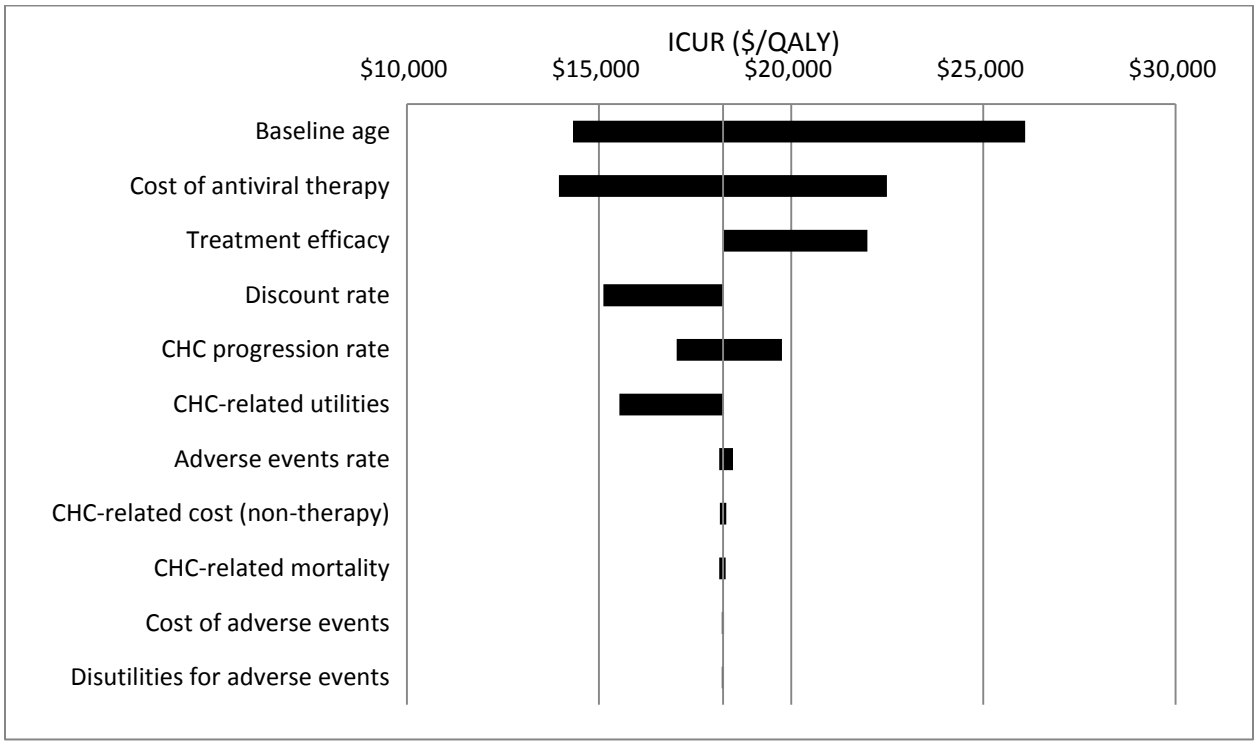

Figure 22: Tornado Diagram: (4) SOF24 + RBV24 Versus PR for Genotype 3 Treatment-Naive Non-cirrhotic Patients (ICUR $ 154,599 /QALY)

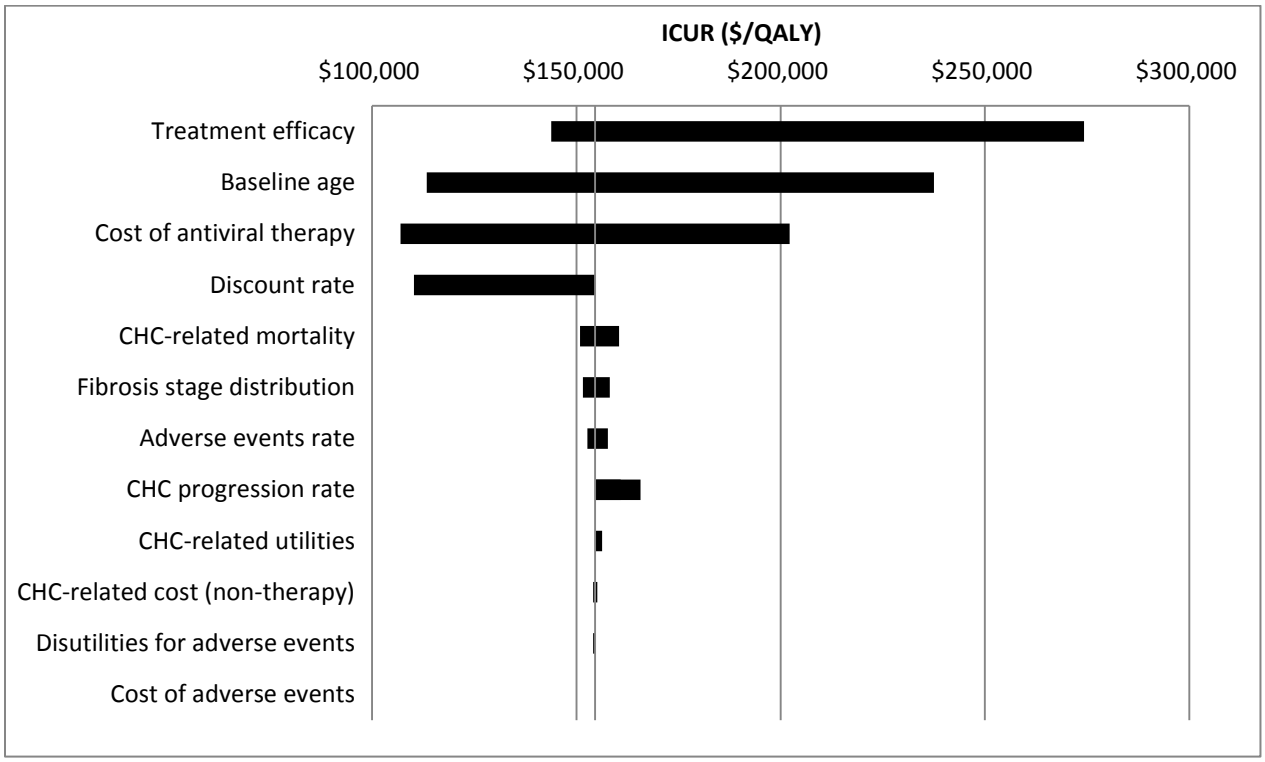

Figure 23: Tornado Diagram: (4) SOF24 + RBV24 Versus PR for Genotype 3 Treatment-Naive Cirrhotic Patients (ICUR $ 92,117 /QALY)

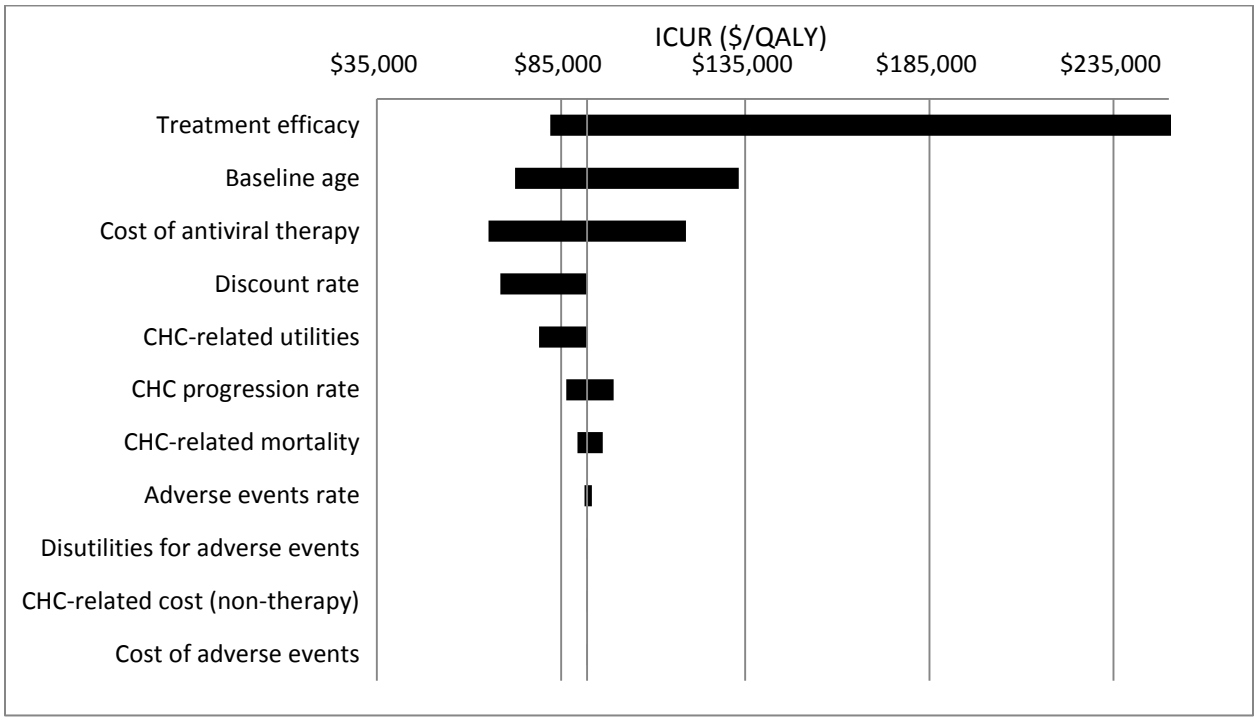

Figure 24: Tornado Diagram: (40) So12 PR12 Versus No Treatment for Genotype 3 Treatment-Experienced Non-cirrhotic Patients (ICUR $ 19,339 /QALY)

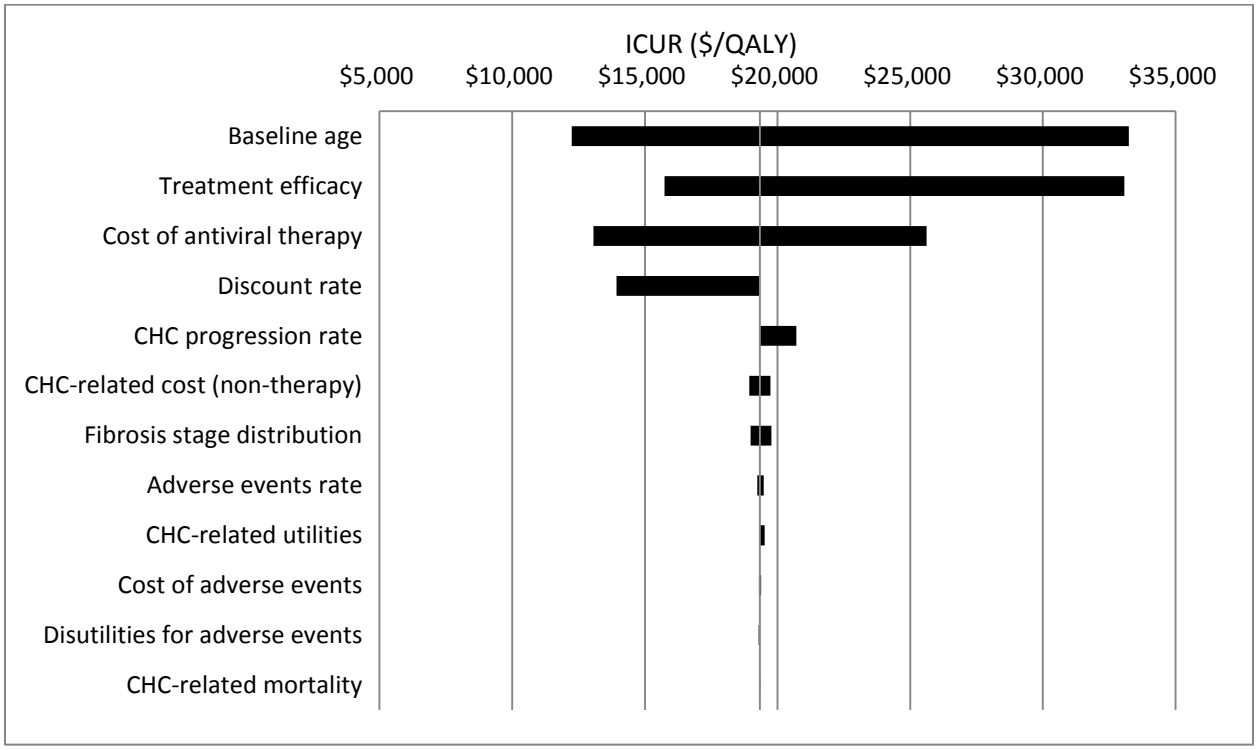

Figure 25: Tornado Diagram: (40) So12 PR12 Versus No Treatment for Genotype 3 Treatment-Experienced Cirrhotic Patients (ICUR $ 20,496 /QALY)

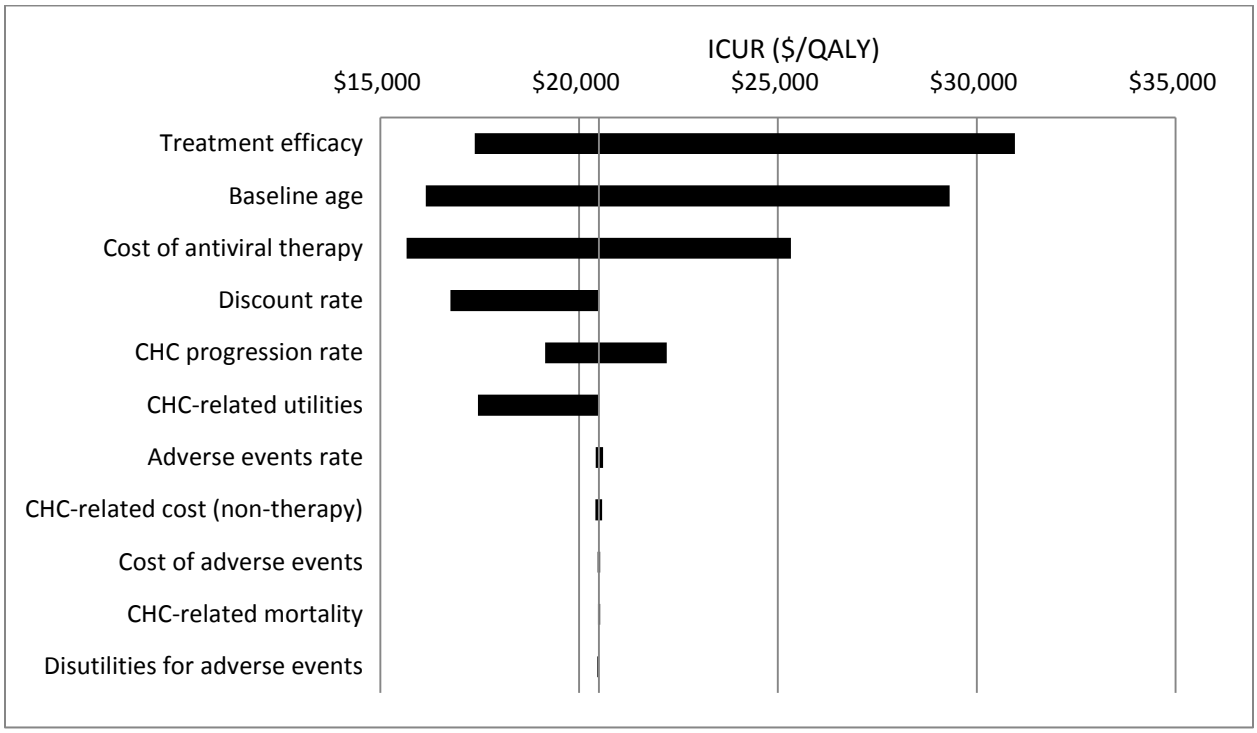

Figure 26: Tornado Diagram: (3) SOF12 + RBV12 Versus PR for Genotype 4 Treatment-Naive Non-cirrhotic Patients (ICUR $ 133,604 /QALY)

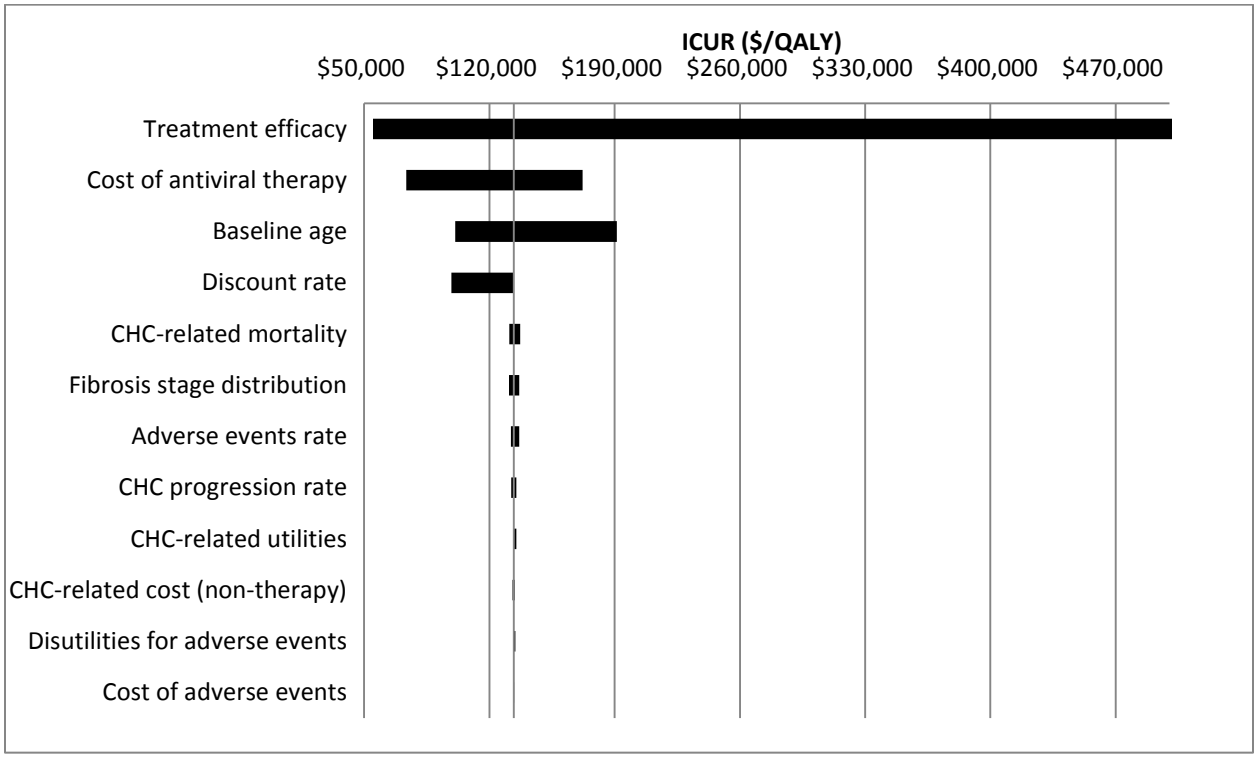

Figure 27: Tornado Diagram: (4) SOF24 + RBV24 Versus PR for Genotype 4 Treatment-Naive Cirrhotic Patients (ICUR $ 59,492 /QALY)

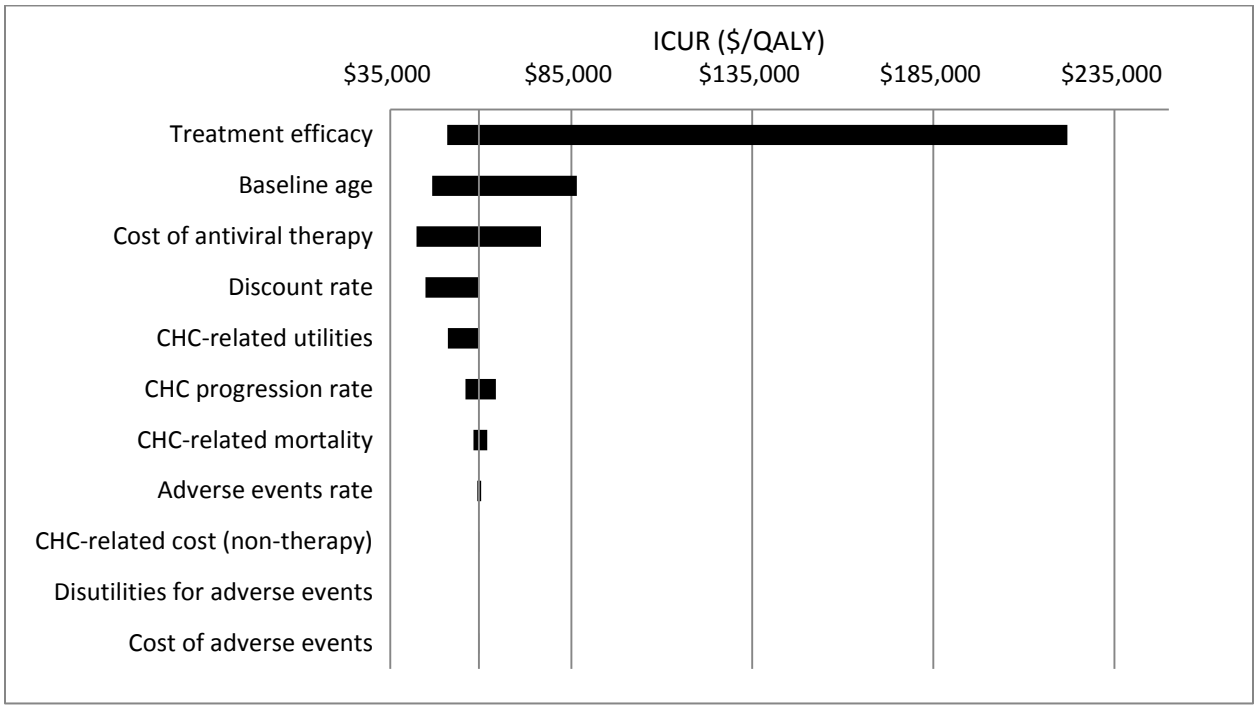

Figure 28: Tornado Diagram: (3) SOF12 + RBV12 Versus No Treatment for Genotype 4 Treatment-Experienced Non-cirrhotic Patients (ICUR $ 29,314 /QALY)

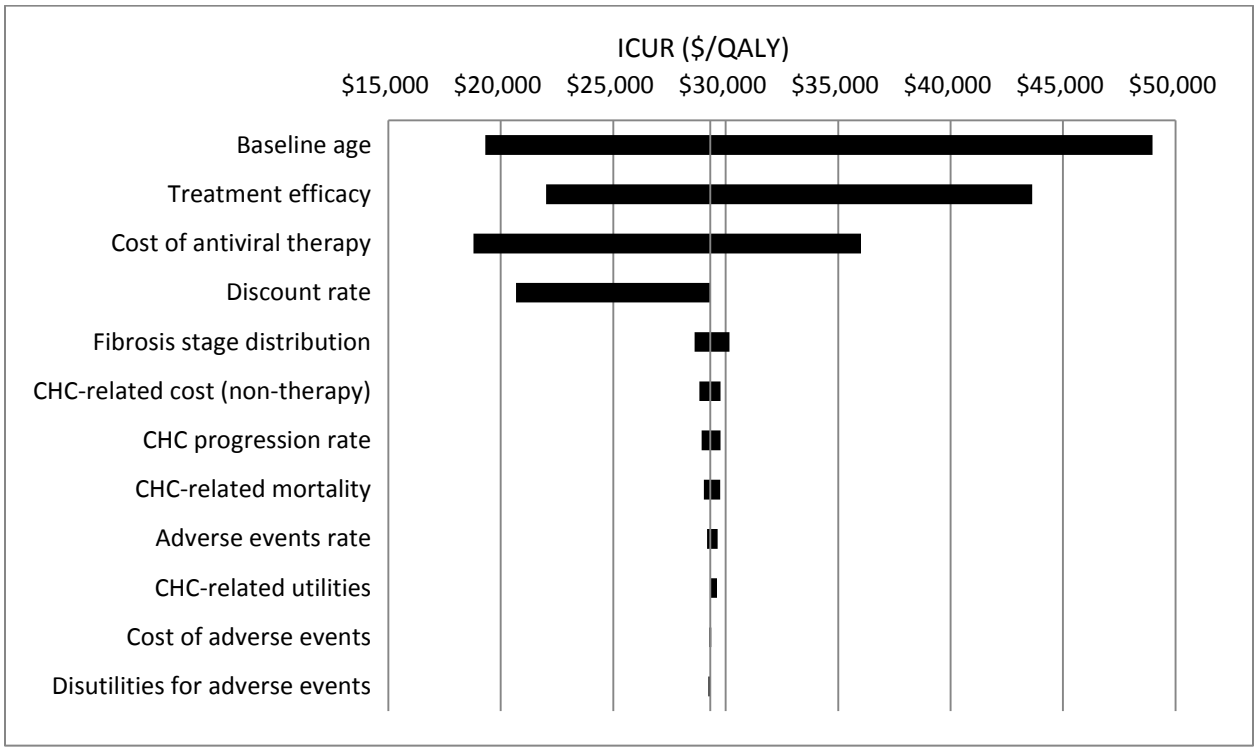

Figure 29: Tornado Diagram: (3) SOF12 + RBV12 Versus No Treatment for Genotype 4 Treatment-Experienced Cirrhotic Patients (ICUR $ 26,982 /QALY)