Cost-effectiveness of currently recommended direct-acting antiviral treatments in patients infected with genotypes 1 or 4 hepatitis C virus in the US

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ABSTRACT

Objective: This study compared the cost-effectiveness of direct-acting antiviral therapies currently recommended for treating genotypes (GT) 1 and 4 chronic hepatitis C (CHC) patients in the US. Methods: A cost-effectiveness analysis of treatments for CHC from a US payer’s perspective over a lifelong time horizon was performed. A Markov model based on the natural history of CHC was used for a population that included treatment-naive and -experienced patients. Treatment alternatives considered for GT1 included ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin (3D±R), sofosbuvir + ledipasvir (SOF/LDV), sofosbuvir + simprevir (SOF + SMV), simprevir + pegylated interferon/ribavirin (SMV + PR) and no treatment (NT). For GT4 treatments, ombitasvir/paritaprevir/ritonavir + ribavirin (2D + R), SOF/LDV and NT were compared. Transition probabilities, utilities and costs were obtained from published literature. Outcomes included rates of compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and liver-related death (LrD), total costs, life-years and quality-adjusted life-years (QALYs). Costs and QALYs were used to calculate incremental cost-effectiveness ratios.

Results: In GT1 patients, 3D ± R had the lowest costs and highest QALYs. In GT4 patients, 2D + R had lower rates of liver morbidity and mortality, lower cost and more QALYs than SOF/LDV and NT.

Limitations: While the results are based on input values, which were obtained from a variety of heterogeneous sources—including clinical trials, the findings were robust across a plausible range of input values, as demonstrated in probabilistic sensitivity analyses.

Conclusions: Among currently recommended treatments for GT1 and GT4 in the US, 3D ± R (for GT1) and 2D + R (for GT4) have a favorable cost-effectiveness profile.

Introduction

Hepatitis C virus (HCV) is a blood-borne infection that can lead to cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and liver-related death (LRD).1,2 The prevalence of chronic HCV infection is estimated to be between 2.7–5.2 million people,3,4 making it the most common blood-borne infection in the US. Genotype 1 (GT1) is the most common HCV genotype in the US.5 The prevalence of more advanced liver disease is expected to increase, as well as the total cost associated with chronic HCV infection.6 Chronic hepatitis C (CHC) currently costs the US healthcare system ~$6.5 billion annually and is expected to reach $9.1 billion by 2024.6

The marker for cure of HCV infection, sustained virologic response (SVR), defined as undetectable viral load at least 12 weeks after completion of therapy, may halt HCV disease progression. Numerous trials have reported high SVR rates in novel direct-acting antivirals (DAAs) therapies.

In particular, several sofosbuvir (SOF)-based regimens were approved by the US Food and Drug Administration (FDA) as the first DAA treatments in the past few years. These regimens have demonstrated high efficacy compared to older therapies, such as protease inhibitor-based or peg-interferon-based regimens, and a number of studies have compared the cost-effectiveness of SOF-containing regimens to older therapies. For example, Saab et al.8 found SOF + pegylated interferon/ribavirin (SOF + PR) to be more cost-effective than other therapies in GT1. Hagan et al.9 reported SOF + simprevir (SOF + SMV) to have lower costs and more quality-adjusted life-years (QALYs) compared to SOF + ribavirin (SOF + R) in GT1. In other studies, SOF + ledipasvir (SOF/LDV) has been reported to be an optimal strategy in GT 1 depending on its cost, but not in other genotypes.9,10

Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin (3D ± R) was approved by the FDA for treating GT1 patients in the US in December 2014 and ombitasvir/paritaprevir/ritonavir + ribavirin (2D + R) for treating genotype 4 (GT4) non-cirrhotic HCV patients in July 2015. Based on the American Association for the Study of Liver Diseases (AASLD) and the
Infectious Diseases Society of America (IDSA) guidelines, DAAAs recommended for treating GT1 patients include 3D ± R, SOF/LDV, SOF + SMV and simeprevir + pegylated interferon/ribavirin (SMV + PR); and 2D + R and SOF/LDV for GT4.

There have been no published data comparing the cost-effectiveness of the currently recommended DAA regimens for treating GT1 or GT4 HCV patients in the US. The purpose of this study is to fill this gap in the literature. Specifically, we sought to compare the lifetime costs, liver outcomes, quality-adjusted life years (QALYS), and overall cost-effectiveness in patients with GT1 or GT4.

**Methods**

A cost-effectiveness analysis of treatments for CHC from the US healthcare system perspective with a lifetime horizon over annual cycles was performed.

**Natural history of HCV**

A Markov state-transition model was developed based on the natural history of CHC from Liu et al. (Figure 1). The model characterized different health states associated with the disease based on liver histology and clinical characteristics. Health states included five early stages of CHC based on METAVIR score [no fibrosis (F0), portal fibrosis with no septa (F1), portal fibrosis with few septa (F2), numerous septa without cirrhosis (F3), and compensated cirrhosis (CC, F4)], a spontaneous clearance state (No HCV), three SVR states [recovered-history of mild disease (F0 or F1), recovered-history of moderate disease (F2 or F3), recovered-history of compensated cirrhosis (F4)], decompensated cirrhosis (DCC), HCC, liver transplant (LT), and two absorbing mortality states (LrD and ccMTC). The model did not include fibrosis stage improvement (i.e. regression) after achieving SVR.

During the non-fibrosis progression phase, patients with cirrhosis faced the risk of transitioning to HCC or DCC. Cirrhotic patients who achieved SVR also faced the risk of progressing to HCC. Patients with HCC or DCC could receive liver transplants. For all patients who achieved SVR, HCV re-infection was possible. Re-infected patients were assumed to transition back to their respective fibrosis state prior to achieving SVR, and then progress through the most severe health states at the same rate as untreated patients. Mortality rates were derived from the US life tables.

**Study population and treatment comparisons**

Guidelines-recommended regimens for HCV differ by genotype. For that reason we conducted separate analyses for populations with GT1 and GT4. For GT1 (any METAVIR score) the treatment regimens included in the analysis were 3D ± R, SOF/LDV, SOF + SMV, SMV + PR, and no treatment (NT). The analyses for the GT4 population were restricted to non-cirrhotic HCV patients (METAVIR stages F0–F3) because efficacy data were not available for 2D + R in the cirrhotic population at the time this analysis was conducted. The treatment regimens compared were 2D + R, SOF/LDV and NT.

**Patient baseline characteristics**

Patient characteristics for each cohort on entry to the model (start of treatment) were based on pooled data from the

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Figure 1. Health state transition model. Health states are depicted by ellipses, while arrows represent permissible transitions between health states (hashed arrows depict the possibility of achieving SVR and dotted arrows depict a potential reinfection). Note: Model also includes HCC and liver transplant health states for first and subsequent years in those conditions.
Table 1. Transition-state probabilities, costs, and health-utilities.

| Variable | Base value | Source |
|----------|-----------|--------|
| **Transition state probabilities** | | |
| **Fibrosis progression** | | |
| **Males** | | |
| <40 | 0.050 | Assumed equal 40–49 |
| 40–49 | 0.050 | Liu et al.12 |
| 50–59 | 0.120 | Liu et al.12 |
| 60–69 | 0.200 | Liu et al.12 |
| 70–79 | 0.260 | Liu et al.12 |
| ≥80 | 0.371 | Interpolated from 70–79 |
| **Females** | | |
| <40 | 0.030 | Assumed equal 40–49 |
| 40–49 | 0.030 | Liu et al.12 |
| 50–59 | 0.060 | Liu et al.12 |
| 60–69 | 0.110 | Liu et al.12 |
| 70–79 | 0.140 | Liu et al.12 |
| ≥80 | 0.200 | Liu et al.12 |
| **Non-fibrosis progression** | | |
| Recovered (SVR), no HCV, history of severe fibrosis (CC) to HCC | 0.012 | Cardoso et al.14 |
| CC to DCC | 0.040 | Liu et al.12 |
| CC to HCC (first year) | 0.020 | Liu et al.12 |
| DCC to HCC (first year) | 0.020 | Liu et al.12 |
| **LT** | | |
| DCC to LT (first year) | 0.050 | Liu et al.12 |
| HCC to LT (first year) | 0.150 | Liu et al.12 |
| **Liver-related mortality** | | |
| DCC to liver death | 0.260 | Liu et al.12 |
| HCC first year to liver death | 0.720 | Liu et al.12 |
| HCC subsequent year to liver death | 0.250 | Liu et al.12 |
| LT to liver death | 0.140 | Liu et al.12 |
| After LT to liver death | 0.050 | Liu et al.12 |
| **Viral reinfection** | | |
| Spontaneous remission from F0 | 0.012 | Assumed |
| **Costs** | | |
| Direct medical annual costs by health state | | |
| No fibrosis (F0) | $165 | Younossi et al.24 |
| Portal fibrosis (F1) | $165 | Younossi et al.24 |
| Periportal fibrosis (F2) | $165 | Younossi et al.24 |
| Bridging fibrosis (F3) | $165 | Younossi et al.24 |
| Compensated fibrosis (F4) | $760 | Younossi et al.24 |
| No HCV | $0 | Assumed |
| Recovered (SVR), no HCV, history of mild fibrosis | $83 | Younossi et al.24 |
| Recovered (SVR), no HCV, history of moderate fibrosis | $83 | Younossi et al.24 |
| Recovered, no HCV, history of severe fibrosis (CC) | $381 | Younossi et al.24 |
| DCC | $33,314 | McAdam-Marx et al.30 |
| HCC (first year) | $52,248 | McAdam-Marx et al.30 |
| HCC (subsequent years) | $52,248 | McAdam-Marx et al.30 |
| LT (first year) | $201,765 | McAdam-Marx et al.30 |
| LT (subsequent years) | $45,481 | McAdam-Marx et al.30 |
| Treatment-related adverse events | | |
| Anemia | $1259 | Gao et al.31 |
| Rash | $328 | Gao et al.31 |
| Depression | $849 | Gao et al.31 |
| Neutropenia | $523 | Brogan et al.32 |
| Thrombocytopenia | $3616 | Poordad et al.33 |
| Health utilities | | |
| No fibrosis (F0) | 0.980 | Liu et al.12 |
| Portal fibrosis (F1) | 0.980 | Liu et al.12 |
| Periportal fibrosis (F2) | 0.850 | Liu et al.12 |
| Bridging fibrosis (F3) | 0.850 | Liu et al.12 |
| Compensated fibrosis (F4) | 0.790 | Liu et al.12 |
| No HCV | 1.000 | Assumed |
| Recovered (SVR), no HCV, history of mild fibrosis | 1.000 | Liu et al.12 |
| Recovered (SVR), no HCV, history of moderate fibrosis | 0.933 | Liu et al.12 |
| Recovered (SVR), no HCV, history of severe fibrosis (CC) | 0.933 | Liu et al.12 |
| DCC | 0.720 | Liu et al.12 |
| HCC (first year) | 0.720 | Liu et al.12 |
| HCC (subsequent years) | 0.720 | Liu et al.12 |
| LT (first year) | 0.825 | Liu et al.12 |
| LT (second year) | 0.825 | Liu et al.12 |
SAPPHIRE I\textsuperscript{16} and II\textsuperscript{17}; PEARL II\textsuperscript{18}, III\textsuperscript{19}, and IV\textsuperscript{19}; and TURQUOISE II\textsuperscript{20} clinical trials. The average age was 53.6 years and 62.5\% of patients were male in both genotype cohorts. The baseline distributions of patients by treatment history, fibrosis stage, and genotype are shown in Table 2.

**Clinical inputs**

The clinical inputs for treatment efficacy, duration, and adverse events were derived from clinical trials of study drugs (Table 3). The treatment efficacy measure was SVR rates, which was assessed 12 weeks after treatment was completed. In the GT1 analysis, SVR rates were stratified by sub-genotype (i.e. 1a and 1b), treatment history (treatment-na\textsuperscript{ı}ve and -expe-rienced), and cirrhosis status (cirrhotic and non-cirrhotic). The data were then combined based on the baseline distribution of patients based on sub-genotype, treatment history, and cirrhosis status. We refer to the combined rate as the overall SVR.

Incidence rates of treatment-related adverse events (AE), including anemia, rash, depression, grade 3/4 neutropenia, and grade 3/4 thrombocytopenia were obtained from the same clinical trials for each regimen. Outcomes for NT were assumed to be zero (i.e. SVR rates, rates of AE, regimen-related disutility, and cost of treatment).

**Health utilities**

Utility estimates for each health state are shown in Table 1. Health state utilities were based on Liu \textit{et al.}\textsuperscript{12}. SVRs in patients with mild fibrosis, moderate fibrosis, or compensated cirrhosis were associated with increases in health utility of 0.02, 0.083, and 0.143, respectively, from the untreated health state utility (shown as “recovered” in Table 1). This is based on the evidence that SVR increases long-term health utility\textsuperscript{12}. All increases after SVR were assumed to occur in the second model cycle.

Treatment-related utility decrements were generally attributed to adverse effects (Table 3)\textsuperscript{21}. The decrement in utility

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**Table 2.** Baseline patient characteristics.

| Distribution of patients by fibrosis stage | GT1 (%) | GT4 non-cirrhotic (%) |
|------------------------------------------|---------|-----------------------|
| Overall                                  |         |                       |
| No fibrosis (F0)                         | 24.4    | 29.7                  |
| Portal fibrosis (F1)                     | 32.5    | 39.5                  |
| Periportal fibrosis (F2)                 | 15.6    | 19.0                  |
| Bridging fibrosis (F3)                   | 9.5     | 11.8                  |
| Compensated fibrosis (F4)                | 18.1    | 0.0                   |
| Treatment-na\textsuperscript{ı}ve         |         |                       |
| No fibrosis (F0)                         | 26.7    | 30.2                  |
| Portal fibrosis (F1)                     | 35.6    | 40.2                  |
| Periportal fibrosis (F2)                 | 17.0    | 19.2                  |
| Bridging fibrosis (F3)                   | 9.3     | 10.5                  |
| Compensated fibrosis (F4)                | 11.5    | 0.0                   |
| Treatment-experienced                    |         |                       |
| No fibrosis (F0)                         | 20.0    | 28.7                  |
| Portal fibrosis (F1)                     | 26.6    | 38.3                  |
| Periportal fibrosis (F2)                 | 13.1    | 18.8                  |
| Bridging fibrosis (F3)                   | 9.9     | 14.2                  |
| Compensated fibrosis (F4)                | 30.5    | 0.0                   |

*Source: SAPPHIRE I\textsuperscript{16} and II\textsuperscript{17}; PEARL II\textsuperscript{18}, III\textsuperscript{19}, and IV\textsuperscript{19}; and TURQUOISE II\textsuperscript{20} clinical trials.*

**Table 3.** Sustained virologic response, adverse events, drug costs, and regimen-related disutilities.\textsuperscript{a}

| Sustained virologic response rates (%) | GT1 | GT4 non-cirrhotic |
|---------------------------------------|-----|------------------|
| Overall                               |     |                  |
| 3D ± R                                | 97.0| NA               |
| 2D + R                                | NA  | 100.0            |
| SOF/LDV                               | 96.0| 91.5             |
| SOF + SMV                             | 96.1| NA               |
| SMV + PR                              | 71.9| NA               |
| NT                                    | 0.0 | 0.0              |
| Treatment-na\textsuperscript{ı}ve     |     |                  |
| 3D ± R                                | 97.0| NA               |
| 2D + R                                | NA  | 100.0            |
| SOF/LDV                               | 96.1| 84.6             |
| SOF + SMV                             | 96.7| NA               |
| SMV + PR                              | 78.4| NA               |
| NT                                    | 0.0 | 0.0              |
| Treatment-experienced                 |     |                  |
| 3D ± R                                | 97.1| NA               |
| 2D + R                                | NA  | 100.0            |
| SOF/LDV                               | 96.1| 84.6             |
| SOF + SMV                             | 96.7| NA               |
| SMV + PR                              | 78.4| NA               |
| NT                                    | 0.0 | 0.0              |

| Treatment-related AE rates (%)        | GT1 | GT4 non-cirrhotic |
|---------------------------------------|-----|------------------|
| Overall                               |     |                  |
| Anemia                                |     |                  |
| 3D ± R                                | 4.5 | NA               |
| 2D + R                                | NA  | 1.6              |
| SOF/LDV                               | 0.4 | 0.0              |
| SOF + SMV                             | 1.1 | NA               |
| SMV + PR                              | 18.7| NA               |
| NT                                    | 0.0 | 0.0              |
| Rash                                  |     |                  |
| 3D ± R                                | 8.1 | NA               |
| 2D + R                                | NA  | 3.8              |
| SOF/LDV                               | 3.6 | 0.0              |
| SOF + SMV                             | 8.1 | NA               |
| SMV + PR                              | 28.5| NA               |
| NT                                    | 0.0 | 0.0              |
| Depression                            |     |                  |
| 3D ± R                                | 0.8 | NA               |
| 2D + R                                | NA  | 3.7              |
| SOF/LDV                               | 0.0 | 0.0              |
| SOF + SMV                             | 0.0 | NA               |
| SMV + PR                              | 0.0 | NA               |
| NT                                    | 0.0 | 0.0              |
| Neutropenia                           |     |                  |
| 3D ± R                                | 0.2 | NA               |
| 2D + R                                | NA  | 2.3              |
| SOF/LDV                               | 0.2 | 0.0              |
| SOF + SMV                             | 0.0 | NA               |
| SMV + PR                              | 15.1| NA               |
| NT                                    | 0.0 | 0.0              |
| Thrombocytopenia                      |     |                  |
| 3D ± R                                | 0.2 | NA               |
| 2D + R                                | NA  | 0.0              |
| SOF/LDV                               | 0.5 | 0.0              |
| SOF + SMV                             | 0.0 | NA               |
| SMV + PR                              | 0.0 | NA               |
| NT                                    | 0.0 | 0.0              |

*continued*
Table 3. Continued

| Depression | GT1 | GT4 non-cirrhotic |
|------------|-----|------------------|
| NT         | 0.0 | 0.0              |
| Neutropenia|     |                  |
| 3D ± R     | 0.4 | NA               |
| 2D ± R     | NA  | 2.4              |
| SOF/LDV    | 0.0 | NA               |
| SOF + SMV  | 0.0 | NA               |
| SMV + PR   | 0.0 | NA               |
| NT         | 0.0 | 0.0              |
| Thrombocytopenia |     |                  |
| 3D ± R     | 0.2 | NA               |
| 2D ± R     | NA  | 2.4              |
| SOF/LDV    | 0.4 | NA               |
| SOF + SMV  | 0.0 | NA               |
| SMV + PR   | 15.2| NA               |
| NT         | 0.0 | 0.0              |

Treatment-experienced

| Anemia | GT1 | GT4 non-cirrhotic |
|--------|-----|------------------|
| 3D ± R | 5.4 | NA               |
| 2D ± R | NA  | 0.0              |
| SOF/LDV| 0.3 | NA               |
| SOF + SMV| 1.9| NA               |
| SMV + PR| 15.6| NA               |
| NT     | 0.0 | 0.0              |
| Rash   |     |                  |
| 3D ± R | 8.4 | NA               |
| 2D ± R | NA  | 2.0              |
| SOF/LDV| 3.0 | NA               |
| SMV + PR| 8.8| NA               |
| SMV + PR| 25.0| NA               |
| NT     | 0.0 | 0.0              |
| Neutropenia |     |                  |
| 3D ± R | 1.8 | NA               |
| 2D ± R | NA  | 6.1              |
| SOF/LDV| 0.0 | NA               |
| SOF + SMV| 0.0| NA               |
| SMV + PR| 0.0 | NA               |
| NT     | 0.0 | 0.0              |
| Thrombocytopenia |     |                  |
| 3D ± R | 0.1 | NA               |
| 2D ± R | NA  | 0.0              |
| SOF/LDV| 1.2 | NA               |
| SOF + SMV| 0.0| NA               |
| SMV + PR| 15.0| NA               |
| NT     | 0.0 | 0.0              |

Drug costs ($)\(^{1}\)\(^{b}\)

| Overall | GT1 | GT4 non-cirrhotic |
|---------|-----|------------------|
| 3D ± R  | 87,134 | NA               |
| 2D + R  | NA  | 78,010           |
| SOF/LDV | 95,571| 94,500           |
| SOF + SMV| 177,562| NA               |
| SMV + PR| 92,680| NA               |
| NT      | 0   | 0                |
| Treatment-naïve |     |                  |
| 3D ± R  | 83,728| NA               |
| 2D + R  | NA  | 78,010           |
| SOF/LDV | 86,657| 94,500           |
| SOF + SMV| 167,597| NA               |
| SMV + PR| 87,024| NA               |
| NT      | 0   | 0                |

\(^{a}\)Sources of data except drug costs: (1) for 3D ± R: SAPPHIRE I\(^{18}\) and II\(^{19}\); PEARL II\(^{20}\), III\(^{21}\), and IV\(^{22}\); and TURQUOISE II\(^{23}\); (2) for 2D + R: PEARL I\(^{24}\); (3) for SOF/LDV: ION-1\(^{25}\), ION-2\(^{26}\), ION-3\(^{27}\), and Abergel et al.\(^{28}\); (4) for SOF + SMV: COSMOS\(^{29}\), and (5) for SMV + PR: QUEST-1\(^{30}\), QUEST-2\(^{31}\).

\(^{b}\)Drugs costs obtained from the 2015 Redbook\(^{22}\). These are average costs based on average duration of therapy in the respective population (i.e. overall, treatment-naïve, and treatment-experienced).

was applied for the duration of time that a patient was on therapy. Treatment disutilities for 3D ± R and 2D + R were derived based on EQ-5D utility data from related trials. Due to lack of data availability, regimen-related disutility for SOF + SMV and SOF/LDV was assumed to be equal to the average annualized on-treatment disutility of 3D ± R and 2D + R adjusting for treatment duration. The treatment-related decrements for SMV + PR were taken from a health technology assessment\(^{9}\).

Costs

Only direct medical costs were considered. These included the costs for the regimen, health-state related costs for medical treatment, and adverse event costs (Table 1). All costs in the model were adjusted to 2015 dollars using the consumer price index (medical component) from the US Bureau of Labor Statistics\(^{22}\).

Drug costs were based wholesale acquisition cost (WAC) obtained from the 2015 Redbook\(^{23}\) and calculated as the sum product of daily WAC for each component of the regimen and the mean duration of treatment (in days). The latter was obtained from the clinical trials previously mentioned for each treatment included in the model.

Health state medical costs were defined as annual HCV-related costs for a patient in a given health state and...
included inpatient and outpatient visits, diagnostic and laboratory testing, other medications and procedures, and other direct medical costs. Costs of recovered states (after SVR) were assumed to be 50% lower than otherwise.

The costs for treating AEs associated with treatment were obtained from the published literature. Total costs or adverse events in the model are calculated as the product of the adverse event rate and the adverse event cost.

**Analyses**

Costs and outcomes were discounted by 3% annually. For each cohort of interest (GT1 and GT4), model outcomes included lifetime costs, life years, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) and lifetime risk of CC, DCC, HCC, LT, and LrD.

Probabilistic sensitivity analyses (PSA) were performed to examine the uncertainty surrounding the cost-effectiveness estimates. Variables that were varied in the PSA were baseline patient characteristics, transition probabilities, costs, health utilities, SVR rates, and adverse event rates. SVR and AE rates were assumed to vary ±1.96-times their standard errors (Supplemental Table A1).

Results from the PSA were summarized in the cost-effectiveness acceptability curves (CEACs). For each CEAC, 500 Monte Carlo simulations were conducted using standard assumptions on the parametric distribution for each variable (i.e. dirichlet for fibrosis distribution, gamma distribution for age, beta distribution for probabilities, normal, or gamma distribution for costs).

Deterministic sensitivity analyses (DSA) assessed parameter uncertainty by individually varying the following inputs at low and high values while leaving other inputs at their base case value: SVR rate, AE rate, patient baseline characteristics (including gender, age, and fibrosis distribution), transition probabilities, health-state costs, utilities, and discount rate (Supplemental Table A1). SVR and AE rates were assumed to vary ±1.96-times their standard errors. The results of the DSA were generated using the net monetary benefit (NMB) approach assuming a payer willingness-to-pay of $100,000. The results of the DSA are summarized in tornado diagrams presenting the 20 most influential parameters.

**Results**

**Liver disease outcomes**

Percentages of patients who ever experienced CC, DCC, HCC, LT, or LrD over the lifetime are shown in Table 4. As expected, patients who were not treated were more likely to experience a liver event. On average, liver-related mortality in patients treated with 3D±R or SOF-based regimens was at least 74% lower than that in those who were untreated in the GT1 cohort; and liver-related mortality in patients treated with 2D+R was over 80% lower compared to those who were untreated in the GT4 cohort. Compared to NT, the number needed to treat (NNT) with 3D±R or SOF-based regimens to prevent one LrD was ~3.6 in the GT1 cohort. In the GT4 cohort, compared to NT, the number needed to treat to avoid one LrD was 4.1 for SOF/LDV and 3.8 for 2D+R.

In the GT1 population treated with DAA regimens, 3D±R was associated with the lowest rates of all lifetime liver disease outcomes, and SMV+PR was associated with the highest rates of liver events (Table 4). Rates for SOF+SMV and SOF/LDV were similar to 3D±R.

In the GT4 cohort, 2D+R was associated with lower risks of liver disease across all outcomes compared with SOF/LDV. 2D+R also produced an 82% lower rate of CC and an 88% lower rate of LrD compared to NT.

**Cost-effectiveness**

Results for total costs, life-years, QALYs, and cost-effectiveness of treatment options are summarized in Table 5, where we present the results for the overall, treatment-naïve, and treatment-experienced patient cohorts separately. NT was associated with the lowest total lifetime cost of $48,264 in the overall GT1 population. Total lifetime cost per patient among DAA treatment options ranged from a low of $100,282 for 3D±R to a high of $190,682 for SOF+SMV. Among all the treatment options, NT was associated with the lowest QALYs (13.08), and 3D±R and SOF+SMV with the highest QALYs (16.20). Among all DAA regimens in the GT1 population, 3D±R had the lowest ICER compared to NT ($16,677 per QALY). 3D±R was also the least costly regimen that offered the highest QALYs, i.e. it dominated the other DAA treatment options in the overall GT1 cohort (Figure 2). The cost per SVR was $103,410 for 3D±R, which was also the lowest among the treatment options. The cost per SVR for SOF/LDV, SMV+PR, and SOF+SMV was $113,358, $161,515, and $198,421, respectively (Table 5). Similarly, in treatment-naïve patients, 3D±R dominated all the DAA treatment options. In treatment-experienced patients, 3D±R dominated SOF/LDV and SMV+PR. SOF+SMV conferred a higher QALY, but was more costly: its ICER vs 3D±R was $5,132,925 per QALY, well above the traditional willingness-to-pay per QALY threshold in the US.

In GT4 patients, 2D+R dominated SOF/LDV and NT in all patient segments (Table 5). Specifically, in the overall patient cohort, NT had the lowest total cost ($36,407) and the lowest life-years (16.01) and QALYs (14.00). 2D+R had a lower cost compared to SOF/LDV ($83,301 vs $102,355) and produced more QALYs (16.83 vs 16.59). The cost per SVR for 2D+R and SOF/LDV was $83,301 and $111,812, respectively.

**Sensitivity analysis**

The PSA was conducted to assess the robustness of our results over a plausible range of values of inputs in the model. The PSA results for the GT1 cohort showed that at a willingness-to-pay threshold less than $18,000 per QALY, NT is the preferred option, and at a willingness-to-pay threshold above $18,000, 3D±R is the preferred option (Figure 3). None of the other treatment options was preferred at any given willingness-to-pay threshold. The PSA results for the GT4 analysis were similar (Figure 4). At a willingness-to-pay threshold...
less than $18,000 per QALY NT is the preferred option, but at a willingness-to-pay threshold above $18,000, 2D + R is the preferred option. For completeness, PSA analyses were conducted in treatment-naïve and -experienced GT1 and non-cirrhotic GT4 cohorts presented in Supplemental Figures A1–A4.

### Table 4. Lifetime liver outcome rates by treatment.

| Outcomes (%) | CC | DCC | HCC | LT | LrD |
|--------------|----|-----|-----|----|----|
| Overall GT1  |    |     |     |    |    |
| NT           | 78.3 | 30.3 | 16.7 | 7.1 | 36.7 |
| SMV + PR     | 41.7 | 12.1 | 9.2  | 3.3 | 16.7 |
| SOF/LDV      | 31.2 | 5.2  | 7.0  | 1.9 | 9.4  |
| SOF + SMV    | 31.2 | 5.1  | 7.0  | 1.9 | 9.4  |
| 3D ± R       | 30.2 | 5.0  | 6.8  | 1.9 | 9.2  |
| Treatment-naïve GT1 |    |     |     |    |    |
| NT           | 76.5 | 29.0 | 16.0 | 6.7 | 34.9 |
| SMV + PR     | 34.0 | 10.1 | 7.3  | 2.6 | 13.5 |
| SOF/LDV      | 25.3 | 5.0  | 5.4  | 1.6 | 7.9  |
| SOF + SMV    | 26.0 | 5.1  | 5.5  | 1.6 | 8.1  |
| 3D ± R       | 24.9 | 4.9  | 5.3  | 1.6 | 7.8  |
| Treatment-experienced GT1 |    |     |     |    |    |
| NT           | 81.9 | 33.0 | 18.3 | 7.8 | 40.5 |
| SMV + PR     | 55.4 | 15.3 | 12.8 | 4.4 | 22.3 |
| SOF/LDV      | 41.9 | 5.3  | 9.9  | 2.5 | 12.1 |
| SOF + SMV    | 41.5 | 5.2  | 9.8  | 2.5 | 11.9 |
| 3D ± R       | 40.6 | 5.3  | 9.7  | 2.5 | 11.9 |
| Overall GT4 non-cirrhotic |    |     |     |    |    |
| NT           | 73.5 | 26.0 | 14.3 | 5.9 | 30.4 |
| SOF/LDV      | 18.3 | 5.4  | 3.0  | 1.2 | 6.1  |
| 2D + R       | 13.2 | 3.5  | 1.9  | 0.7 | 3.8  |
| Treatment-naïve GT4 non-cirrhotic |    |     |     |    |    |
| NT           | 73.5 | 26.2 | 14.5 | 6.0 | 30.8 |
| SOF/LDV      | 16.4 | 4.8  | 2.6  | 1.0 | 5.3  |
| 2D + R       | 13.6 | 3.7  | 2.0  | 0.8 | 4.0  |
| Treatment-experienced GT4 non-cirrhotic |    |     |     |    |    |
| NT           | 74.0 | 26.1 | 14.4 | 5.9 | 30.4 |
| SOF/LDV      | 22.3 | 6.9  | 3.8  | 1.5 | 7.8  |
| 2D + R       | 12.9 | 3.4  | 0.9  | 0.7 | 3.7  |

The results of the DSA comparing 3D ± R to SOF/LDV in GT1 and 2D + R to SOF/LDV in non-cirrhotic GT4 are presented for overall, treatment-naïve, and -experienced cohorts. In GT1 patients, SOF/LDV SVR rates have the largest impact on the incremental NMB (INMB) values ranging from $–2421 to $28,196; all other parameters generate positive INMB values (see Figure 5; positive values indicate that 3D ± R is more cost-effective, negative values that SOF/LDV is more cost-effective). For the GT4 non-cirrhotic cohort, all 20 scenarios produced positive INMB values in favor of 2D + R, which are contained in the $10,436–$105,982 interval, with SOF/LDV SVR rates having the largest impact (Figure 6). For completeness, PSA analyses were conducted in treatment-naïve and -experienced GT1 and non-cirrhotic GT4 cohorts presented in Supplemental Figures A5–A8. In GT1 treatment-naïve patients, SOF/LDV SVR rates have the largest impact on the results, with a range of INMB of $–6746 to $19,853 (see Supplemental Figure A5); in four other comparisons, the parameters could affect conclusions. For the GT1 treatment-experienced cohort, all 20 scenarios produced positive INMB values favoring 3D ± R, with the range of INMB values contained in the $9816–$39,658 interval (Supplemental Figure A6). In both non-cirrhotic GT4 treatment-naïve and -experienced cohorts, all 20 scenarios produced positive INMB with respective ranges of $9653–$82,668 and $11,830–$151,032 (Supplemental Figures A7 and A8).

### Discussion

Our study results showed that in the US GT1 and GT4 CHC populations, 3D ± R and 2D + R, respectively, are not only

### Table 5. Total costs, life-years, QALYs, and cost-effectiveness of treatments.

| Total cost ($) | Life-years | QALYs | ICER $ (vs no treatment) | ICER $ (other treatments vs 3D ± R) | Cost per SVR ($) |
|----------------|------------|-------|--------------------------|-----------------------------------|------------------|
| Overall GT1    |            |       |                          |                                   |                  |
| NT             | 48,264     | 15.17 | 13.08                    |                                   |                  |
| 3D ± R         | 100,282    | 16.93 | 16.20                    | 16,677                            |                  |
| SOF/LDV        | 108,839    | 16.93 | 16.18                    | 19,538                            | Dominated*       |
| SOF + SMV      | 116,109    | 16.41 | 15.28                    | 30,838                            | Dominated        |
| 3D ± R         | 100,282    | 16.93 | 16.20                    | 16,677                            |                  |
| Treatment-naïve GT1 |        |       |                          |                                   |                  |
| NT             | 43,974     | 15.82 | 13.75                    |                                   |                  |
| 3D ± R         | 94,594     | 17.45 | 16.76                    | 16,798                            |                  |
| SOF/LDV        | 97,586     | 17.45 | 16.75                    | 17,871                            | Dominated        |
| SOF + SMV      | 105,653    | 17.06 | 16.08                    | 30,492                            | Dominated        |
| 3D ± R         | 106,537    | 17.06 | 16.08                    | 30,492                            | Comparisons      |
| Treatment-experienced GT1 |       |       |                          |                                   |                  |
| NT             | 56,430     | 14.24 | 12.11                    |                                   |                  |
| 3D ± R         | 117,541    | 16.29 | 15.47                    | 18,209                            |                  |
| SOF/LDV        | 140,127    | 16.30 | 15.46                    | 24,991                            | Dominated        |
| SOF + SMV      | 135,095    | 15.54 | 14.16                    | 38,315                            | Dominated        |
| 3D ± R         | 213,357    | 16.31 | 15.49                    | 46,499                            | Dominated        |
| Overall GT4 non-cirrhotic |    |       |                          |                                   |                  |
| NT             | 36,407     | 16.01 | 14.00                    |                                   |                  |
| 2D + R         | 83,301     | 17.38 | 16.83                    | 16,594                            |                  |
| SOF/LDV        | 102,355    | 17.27 | 16.59                    | 25,445                            | Dominate         |
| Treatment-naïve GT4 non-cirrhotic |        |       |                          |                                   |                  |
| NT             | 36,185     | 16.38 | 14.36                    |                                   |                  |
| 2D + R         | 83,431     | 17.77 | 17.21                    | 16,608                            |                  |
| SOF/LDV        | 101,311    | 17.70 | 17.08                    | 24,015                            | Dominated        |
| Treatment-experienced GT4 non-cirrhotic |        |       |                          |                                   |                  |
| NT             | 37,173     | 15.57 | 13.57                    |                                   |                  |
| 2D + R         | 83,218     | 16.97 | 16.40                    | 16,253                            |                  |
| SOF/LDV        | 104,567    | 16.76 | 15.98                    | 28,014                            | Dominated        |

*Dominated means lower costs and higher QALYs compared to reference regimen.*
associated with the lowest lifetime risks of liver morbidity and mortality, but also are the most cost-effective options compared to NT and other recommended novel DAA regimens.

This is the first study comparing the cost-effectiveness of novel DAA HCV treatments, including 3D±R and 2D + R, in both GT1 and GT4 CHC populations, and as such should be of importance to payers in the US who are faced with formulary and coverage decisions for CHC. Compared to older regimens the newer DAA therapies have several advantages, including superior effectiveness. Only one published study has included 3D±R among the treatment options. Zhang et al. found that 3D±R dominated SOF/LDV and other treatments for GT1 in patients without cirrhosis. They also concluded that SOF-based treatments for GT1 were generally not cost-effective due to high costs. In our study, 3D±R and 2D + R were the optimal treatments for GT1 and GT4, respectively.

Many previous cost-effectiveness studies compared DAAs to older interferon-containing regimens. In addition to the analyses in the overall GT1 and GT4 populations, we also examined the cost-effectiveness of SOF + PR and SOF + R, where efficacy and safety data were only available in the treatment-naive patients. Compared with 3D±R, both SOF + PR and SOF + R were more costly and generated fewer QALYs, and were, therefore, dominated in the GT1 treatment-naive sub-population. Results were similar in the treatment-experienced sub-population, although SOF + SMV was not dominated, having a marginally higher incremental

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Figure 2. Scatter plot of total cost and QALYs for DAA regimens in GT1 cohort. For each treatment the point shown represents the total cost and QALYs produced.

Figure 3. Cost-effectiveness acceptability curves for GT1 analysis. Curves shown represent results from Monte Carlo simulations in probabilistic sensitivity analysis of treatment options compared in the GT1 population. Each line (representing a different treatment option) shows the percentage of simulations that option was the most cost-effective at each willingness-to-pay threshold. Note that only options that were estimated to be most cost-effective in at least one simulation appear in figure.
QALY-based $= 21$ patients in the COSMOS trial\textsuperscript{28}, but also having incremental costs $\$100,000$ higher than $3D \pm R$. Similarly, in the GT4 treatment-naïve non-cirrhotic sub-population, $2D + R$ dominated $SOF + PR$ with lower costs and more QALYs.

According to a recent review of the literature, the cost-effectiveness of novel agents for treatment of CHC is contingent upon a variety of factors, including HCV genotype, presence of liver cirrhosis, treatment history, and willingness-to-pay thresholds\textsuperscript{29}. In our study, we included GT1 patients...
with all fibrosis stages, while for GT4 we only included non-cirrhotics, given the trial data availability. These and other characteristics of our model and analyses should be considered when interpreting our results.

Our model is subject to several limitations. First, our model did not consider the potential for patients to regress to a less severe disease state after SVR as in other HCV models. The inclusion of disease regression would further reduce the costs and improve utilities for patients that achieved an SVR. Without counting for additional benefits derived from regression, our modeling approach was conservative.

Second, in our model treatment was only possible during the first cycle of the model and re-treatment was not considered. In actual practice it may be unlikely that a re-infected patient would remain without treatment for life.

Third, many of the input values used in the model were from randomized controlled trials with restricted inclusion criteria and closer monitoring, which may not be transferable to the real world. While long-term liver outcomes were not directly measured in clinical trials, they were extrapolated based on SVR. Despite these limitations, trials are used to make regulatory decisions in the US and are not subject to questions of confounding common to observational studies.

Fourth, cost inputs used in this model were obtained from published sources and may not represent the actual costs faced by payers. For example, payers may negotiate on the prices; the discounts are not usually publicly available, and may vary by payer, and thus were not included in the model.

Also, while costs generally fluctuate over time, geographically, and by provider, direct medical costs in our model were assumed to be constant over time. Moreover, this analysis was conducted from the perspective of the third-party payers, and did not include non-medical or indirect costs. Had such costs been included, the economic benefit of treatment would have been greater.

Last, to understand if these and other limitations of our analysis impacted our findings, we conducted DSA and PSA where inputs were varied across a range of plausible values. This analysis confirmed the robustness of our findings. Nevertheless, caution is advised when generalizing these results as they may differ by settings that affect treatment outcomes such as payer type, individual patient comorbidities and characteristics, treatment administration, and adherence. Until then, our analysis offers US payers important insight on the cost-effectiveness of novel treatments in patients GT1 and GT4 HCV.

Conclusion
Among currently recommended treatments for GT1 and GT4 CHC in the US, 3D + R (for GT1 HCV) and 2D + R (for GT4 HCV) have a favorable cost-effectiveness profile.

Transparency

Declaration of funding
Design, analysis, and financial support of this study were provided by AbbVie.

Declaration of financial/other relationships
SS is employed by the Pfleger Liver Institute at UCLA and is a consultant for AbbVie. He is also a consultant and on the speaker bureau for BMS, Gilead, Merck, and Janssen pharmaceuticals. SJ and SV are employed by Medicus Economics LLC, which received payment from AbbVie to undertake research. HP is a contractor for Medicus Economics LLC. AW, YSG,
and SEM are AbbVie employees and may own AbbVie stock. DM is a former AbbVie employee and may own Abbvie stock. AbbVie is the manufacturer of ombitasvir/paritaprevir/ritonavir, dasabuvir (Viekira Pak™).

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