Cost-effectiveness of elbasvir/grazoprevir use in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease in the United States

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Summary

Among patients with chronic kidney disease (CKD) in the United States, HCV infection causes significant morbidity and mortality and results in substantial healthcare costs. A once-daily oral regimen of elbasvir/grazoprevir (EBR/GZR) for 12 weeks was found to be a safe and efficacious treatment for HCV in patients with CKD. We evaluated the cost-effectiveness of EBR/GZR in treatment-naïve and treatment-experienced CKD patients compared with no treatment (NoTx) and pegylated interferon plus ribavirin (peg-IFN/RBV) using a computer-based model of the natural history of chronic HCV genotype 1 infection, CKD and liver disease. Data on baseline characteristics of the simulated patients were obtained from NHANES, 2000–2010. Model inputs were estimated from published studies. Cost of treatment with EBR/GZR and peg-IFN/RBV were based on wholesale acquisition cost. All costs were from a third-party payer perspective and were expressed in 2015 U.S. dollars. We estimated lifetime incidence of liver-related complications, liver transplantation, kidney transplantation, end-stage liver disease mortality and end-stage renal disease mortality; lifetime quality-adjusted life years (QALY); and incremental cost-utility ratios (ICUR). The model predicted that EBR/GZR will significantly reduce the incidence of liver-related complications and prolong life in patients with chronic HCV genotype 1 infection and CKD compared with NoTx or use of peg-IFN/RBV. EBR/GZR-based regimens resulted in higher average remaining QALYs and higher costs ($11,571.6, $191,242) compared with NoTx ($8,919.9, $156,236) or peg-IFN/RBV ($10,285.7, $186,701). Peg-IFN/RBV is not cost-effective, and the ICUR of EBR/GZR compared with NoTx was $13,200/QALY. Treatment of a patient on hemodialysis with EBR/GZR resulted in a higher ICUR ($217,000/QALY). Assuming a threshold of $100,000 per QALY gained for cost-effectiveness, use of elbasvir/grazoprevir to treat an average patient with CKD can be considered cost-effective in the United States.

KEYWORDS
chronic hepatitis C, chronic kidney disease, CKD, cost-effectiveness analysis, elbasvir/grazoprevir, HCV
1 | INTRODUCTION

The burden of chronic kidney disease (CKD) in terms of increased risk for cardiovascular disease, hospitalizations and mortality is significant. More than 20 million persons are believed to have CKD at varying stages of progression in the United States (US) and approximately 113,000 patients started treatment for end-stage renal disease (ESRD) in 2011. HCV infection is prevalent among CKD patients, with an overall prevalence among haemodialysis patients in the United States of 9.9%. Hepatitis C virus (HCV) infection has been associated with significant morbidity including liver disease-related deaths, and cardiovascular mortality among patients with CKD. The prevalence of HCV in the CKD population is much higher than that of the general population. Treatment options for patients with HCV and CKD (especially stages 4–5) are limited. Most of the currently available all-oral regimens (i) were not evaluated in randomized controlled trials in patients with abnormal kidney function, (ii) are not optimal for patients with patients because they include ribavirin, which is associated with anaemia, or (iii) they contain drugs whose metabolites are cleared by the kidney (such as sofosbuvir). Elbasvir (EBR, NS5A inhibitor)/grazoprevir (GZR, NS3/4A protease inhibitor) were recently studied in the C-SURFER (Hepatitis C: Study to Understand Renal Failure’s Effect on Responses) study, a phase 2/3 double-blind, placebo-control trial in HCV genotype 1 patients with CKD4/5. The study demonstrated that a once-daily oral regimen of EBR/GZR for 12 weeks was safe and can achieve high rates of SVR across many CKD patient subgroups, including those receiving haemodialysis.

The decision to treat HCV in patients with CKD requires weighing the potential health benefits, risks and costs of therapy. The objective of this study was to assess the cost-effectiveness of EBR/GZR in patients with CKD compared with no treatment (NoTX) and pegylated interferon plus ribavirin (peg-IFN/RBV).

2 | METHODS

To represent the natural history of chronic HCV genotype 1 infection, CKD and liver disease, a computer-based, discrete-time, state-transition semi-Markov model was developed and programmed in Microsoft Excel (Microsoft Corp., Redmond, WA). The model is fully parameterized to run the base case and sensitivity analysis. One-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were implemented using Visual Basic macros. The model combines major complications of both CKD and liver disease. The health states for CKD are defined according to the National Kidney Foundation K/DOQI guidelines. The combined models consists of 80 mutually exclusive states representing CKD status (CKD1, CKD2, CKD3a, CKD3b, CKD4, CKD5, HD and KT) and liver disease conditions (SVR-F0-F3; SVR-F4, F0, F1, F2, F3, F4, DC, HCC and LT). In addition, it tracks separately four types of mortality: ESRD mortality, CVD mortality, ESLD mortality and other-cause mortality. The models uses an annual cycle to predict the incidence and progression of CKD and liver disease and complications in a cohort of patients stratified by several baseline characteristics, including sex, age, liver fibrosis status and CKD status.

Some major assumptions in the models are noted below (See also Supplementary Information). Sustained virologic response (SVR) is considered a cure for noncirrhotic patients with no risk of reactivation of HCV infection. Previously cirrhotic patients are assumed to have an excess risk of DC and HCC, even if they achieved SVR. The model combines multiple decompensation outcomes (ie, ascites, variceal haemorrhage and encephalopathy) into a single aggregate DC health state. Progression to DC will only occur in patients with compensated cirrhosis, whereas progression to HCC occurs in patients in F4 and DC states. Liver transplantation is only performed on DC or HCC patients. Successful transplant patients are at no risk of reactivation or progression to liver disease. If a patient fails transplantation, there is no future re-treatment. The model includes currently approved and available treatments. Retreatment with antiviral drugs that are currently available or might become available in the
near future is not considered. Note that patients who progress to DC or those who receive LT do not receive antiviral therapy. However, we acknowledge recent data suggest that some direct-acting agents (DAAs) are efficacious in DC and LT patients. For patients diagnosed with CKD, all cases are managed according to accepted practices. We defined health states for CKD according to GFR only. In the model, CKD3, CKD4 and CKD5 states were not stratified according to albuminuria or proteinuria. Patients staged at CKD5 may not immediately undergo dialysis or receive a kidney transplant. We assumed that all patients progressing from CKD5 or KT start treatment with hemodialysis only and do not utilize peritoneal dialysis. We note that chronic HCV accelerates progression to advanced CKD and CKD death, but not vice versa. We assume that CKD enhances the risk of MI and stroke and death. Finally, concomitant HCV and CKD

**FIGURE 1** (A) State-transition diagram for chronic hepatitis C and liver disease model. The liver disease model consists of the following health states: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant state (LT), end-stage liver disease death (ESLD Death), death from all other causes (not shown here) and two sustained virologic response (SVR) status states stratified by fibrosis stage—“SVR, F0–F3” and “SVR, F4.” (B) Simplified state-transition diagram for the chronic kidney disease (CKD) model. CKD stages are as follows: CKD1 (GFR ≥90), CKD2 (GFR 60-89), CKD3a (GFR 45-59), CKD3b (GFR 30-44), CKD4 (GFR 15-29), stage 5 (GFR<15), hemodialysis (HD) and kidney transplantation (KT)
in CKD patients may progress to (i) more severe HCV disease only; (ii) CKD disease only; or (iii) both. For example, a patient with CKD3a and fibrosis level F0 (CKD3a-F0) can progress to CKD3b-F0, CKD3a-F1, CKD3b-F1, can suffer an MI or stroke, can die from all causes or MI or stroke, or remain in CKD3a-F0.

2.1 | Treatment comparators

The clinical and economic impact of using EBR/GZR was compared against that of no treatment (NoTx), and pegylated interferon (peg-IFN) with ribavirin (RBV) (peg-IFN/RBV) in CKD patients with chronic HCV GT1 infection.

2.2 | Model inputs

CKD model inputs were derived from a targeted review of the published literature (Table 1). HCV model parameters were obtained from our previous studies

2.2.1 | Efficacy

Efficacy of EBR/GZR was obtained from C-SURFER (a randomized, parallel-group, multisite, placebo-controlled trial). In the prespecified primary modified intention to treat analysis of efficacy, the proportion of patients achieving sustained viral response (SVR) 12 weeks after the completion of therapy was 99% (115/116). Efficacy of pegylated interferon (peg-IFN) plus ribavirin (peg-IFN/RBV) of 60% was based on the results of a meta-analysis.

2.2.2 | Mortality

Background, other-cause mortality rates for patients in each CKD stage were assumed to be the same as the age- and sex-specific mortality in the general population obtained from U.S. life tables. Because of high CVD-attributable mortality among patients with CKD, we subtracted the expected CVD mortality rates from the baseline all-cause mortality rates to avoid double counting. Excess disease-related mortality rates as a result of CKD, CVD or liver disease were derived from published literature (Table 1).

2.2.3 | Cardiovascular disease

Patients can have a stroke event or an MI event. Baseline probabilities of MI and stroke are derived from the age- and sex-based Framingham risk equations multiplied by a CKD stage multiplier (Supplementary Information).

2.2.4 | Costs

Costs (inpatient, outpatient and pharmaceutical) of managing CKD by stage are based on a cost function developed by Smith et al.

that used data from members of the Kaiser Permanente Northwest (Portland, Oregon).

2.2.5 | Utilities

Utilities for each disease and stage were derived from the published literature (Table 1). Several methods can be used to describe the utilities for HCV and CKD disease combination: minimum, geometric mean, simple average, weighted average and maximum of the utilities of the two diseases. We combined utilities using the simple average of the two utilities and tested the sensitivity of the results using alternative methods.

2.3 | Model outcomes

We calculated lifetime risk of liver disease complications, life expectancy, discounted treatment costs, discounted health state costs and discounted QALYs. We applied within-cycle correction to all cumulative outcomes using Simpson’s 1/3rd rule and tested sensitivity of the results to the method of correction by applying the standard application of half-cycle correction method. For the cost-effectiveness analysis, we calculated costs and QALYs over the remaining duration of a patient’s lifetime. Cost-effectiveness of an EBR/GZR regimen relative to a comparator was evaluated using the incremental cost-utility ratio (ICUR) obtained by dividing incremental total discounted costs by the incremental total discounted number of QALYs resulting from using EBR/GZR regimen instead of the comparator. We also calculated the incremental cost-effectiveness ratios (ICER) as the ratio of incremental total discounted costs and incremental total discounted number of life year (LY) resulting from using two different regimens.

2.3.1 | Model predictions and validation

The face validity of the model was checked during collaboration with experts from the relevant fields of medicine, in consultation with health economists and decision scientists, and by comparing its structure with that of previously published models. Several tests were built into the model for verification and to ensure internal validity. For example, the sum of the distribution of persons in each health state at the end of each cycle was verified to be equal to 1 both numerically using Microsoft Excel (Microsoft Corp., Redmond, WA) and analytically by transferring the formula into Mathematica (Wolfram Research, Inc., Champaign, IL, USA) and using the built-in algebraic functions within Mathematica to manipulate the resulting expressions.

3 | MODEL ANALYSIS

The model was run for each of the specified patient profiles. Depending on the type of analysis, an overall weighted average of the results was generated based on the distribution of the patient characteristics at the time of treatment assumed for a given analysis.
| Input                                           | Base case value | Range or probability distribution | Source |
|------------------------------------------------|-----------------|-----------------------------------|--------|
| **(a) CKD Model**                              |                 |                                   |        |
| Distribution of CKD stages at baseline         |                 |                                   |        |
| CKD1                                           | 0.393           |                                   | 2,3    |
| CKD2                                           | 0.422           |                                   |        |
| CKD3a                                          | 0.089           |                                   |        |
| CKD3b                                          | 0.089           |                                   |        |
| CKD4                                           | 0.006           |                                   |        |
| CKD5                                           | 0.000           |                                   |        |
| Haemodialysis (HD)                             | 0.000           |                                   |        |
| Kidney transplant (KT)                         | 0.000           |                                   |        |
| **Risk factors for CVD**                       |                 |                                   | 3      |
| Systolic blood pressure (SBP)                  | 135             |                                   |        |
| Total to high-density lipoprotein ratio (TCHDL)| 4.79            |                                   |        |
| Prevalence of smoking                          | 0.62            | 0.568–0.673                       |        |
| Prevalence of diabetes                         | 0.117           | 0.078–0.156                       |        |
| Prevalence of left ventricular hypertrophy (LVH)| 0.16           |                                   |        |
| **Annual transition probabilities**            |                 |                                   |        |
| CKD1 to CKD2                                   | 0.083           |                                   | 35     |
| CKD2 to CKD3a                                  | 0.096           |                                   | 33     |
| CKD3a to CKD3b                                 | 0.096           | Beta(228.42,1438.88)              | 33     |
| CKD3b to CKD4                                  | 0.137           | Beta(110.09,1249.03)              | 20     |
| CKD4 to CKD5                                   | 0.081           | Beta(126.69,75.69)                | 20     |
| CKD5 to HD                                     | 0.626           | Beta(77.08,8487.72)               | 20     |
| CKD5 to KT                                     | 0.009           | Beta(67,16,3467.81)               | 20     |
| HD to KT                                       | 0.019           | Beta(19,34,401.12)                | 20     |
| KT to HD                                       | 0.046           | Beta(105,867.26)                  | 20     |
| CKD5 to death                                  | 0.108           | Beta(348.45,1738.08)              | 20     |
| HD to death                                    | 0.167           | Beta(16,04,556.64)                | 20     |
| KT to death                                    | 0.028           | Beta(23,92,175.41)                | 20     |
| Acute STK to death                             | 0.12            | Beta(27,94,371.2)                 | 17     |
| Acute MI to death                              | 0.07            | Beta(228.42,1438.88)              | 17     |
| **Hazard rates**                               |                 |                                   |        |
| Risk of death given HCV (all stages)           | 1.24            | LogNormal(0.22,0.08)              | 36     |
| Risk of progression of CKD given HCV (all stages)| 1.32          | LogNormal(0.28,0.11)              | 37,38  |
| Risk of MI and stroke (CKD stage 3a)           | 1.40            | LogNormal(0.34,0.02)              | 39     |
| Risk of MI and stroke (CKD stage 3b)           | 2.00            | LogNormal(0.69,0.03)              | 37     |
| Risk of MI and stroke (CKD stage 4)            | 2.80            | LogNormal(1.03,0.03)              | 37     |
| Risk of MI and stroke (CKD stage 5)            | 3.40            | LogNormal(1.22,0.05)              | 37     |
| Risk of all-cause mortality (CKD stage 3a)     | 1.20            | LogNormal(0.18,0.02)              | 37     |
| Risk of all-cause mortality (CKD stage 3b)     | 1.80            | LogNormal(0.59,0.03)              | 37     |
| Risk of all-cause mortality (CKD stage 4)      | 3.20            | LogNormal(1.16,0.02)              | 37     |
| Risk of all-cause mortality ESRD (CKD stage 5, HD)| 5.90          | LogNormal(1.77,0.05)              | 37     |
| **Health state utilities**                     |                 |                                   |        |
| CKD1                                           | 0.900           | Beta(152.76,16.97)                | 40     |
| CKD2                                           | 0.900           | Beta(152.76,16.97)                | 38     |

(continues)
### TABLE 1 (continued)

| Input                          | Base case value | Range or probability distribution | Source |
|-------------------------------|-----------------|------------------------------------|--------|
| CKD3a                         | 0.870           | Beta(198.89,29.72)                 | 38     |
| CKD3b                         | 0.870           | Beta(198.89,29.72)                 | 38     |
| CKD4                          | 0.850           | Beta(229.65,40.53)                 | 38     |
| CKD5                          | 0.700           | Beta(344.97,100.15)                | 16,38  |
| Haemodialysis                 | 0.525           | Beta(729.38,659.91)                | 41     |
| Post-kidney transplant        | 0.840           | Beta(245.02,46.67)                 | 42     |
| One-time cost ($)             |                 |                                    |        |
| Cost of acute MI              | 17 363          | Gamma(7525.02,2.34)                | 43     |
| Cost of acute stroke          | 15 541          | Gamma(6212.33,2.53)                | 41     |
| Cost of kidney transplant     | 104 015         | Gamma(333678.63,0.35)              | 44     |
| Annual cost ($)               |                 |                                    |        |
| CKD1                          | 5133            | Gamma(61.47,83.52)                 | 27     |
| CKD2                          | 5133            | Gamma(61.47,83.52)                 | 27     |
| CKD3a                         | 5171            | Gamma(61.47,84.12)                 | 27     |
| CKD3b                         | 5171            | Gamma(61.47,84.12)                 | 27     |
| CKD4                          | 8692            | Gamma(61.47,141.41)                | 27     |
| CKD5                          | 27 990          | Gamma(61.47,455.37)                | 16     |
| Haemodialysis                 | 96 844          | Gamma(61.47,1575.57)               | 42     |
| Post-kidney transplant        | 12 946          | Gamma(61.47,210.63)                | 45     |
| (b) Liver disease model       |                 |                                    |        |
| Annual Transition Probabilities|                |                                    |        |
| Distribution of METAVIR fibrosis stages at baseline | | | |
| F0                            | 0.107           |                                    | 46     |
| F1                            | 0.357           |                                    |        |
| F2                            | 0.232           |                                    |        |
| F3                            | 0.143           |                                    |        |
| F4                            | 0.161           |                                    |        |
| Fibrosis progression          |                 |                                    | 47     |
| F0 to F1                      | 0.117           | Beta(2.3,11.33)                    |        |
| F1 to F2                      | 0.085           | Beta(1.64,10.6)                    |        |
| F2 to F3                      | 0.120           | Beta(10.02,35.53)                  |        |
| F3 to F4/Compensated Cirrhosis| 0.116           | Beta(4.48,24.22)                   |        |
| F4 to DC                      | 0.029           | Beta(14.89,498.62)                 | 48–52  |
| F4 to HCC                     | 0.028           | Beta(2.43,84.41)                   | 46–56  |
| DC to HCC                     | 0.068           | Beta(23.51,322.19)                 | 57     |
| SVR, F4 to DC                 | 0.008           | Beta(0.84,103.66)                  | 58     |
| SVR, F4 to HCC                | 0.005           | Beta(0.5,251.98)                   | 56     |
| Probability of Receiving a Liver Transplant | | | |
| DC                            | 0.023           | Beta(1.42,87.06)                   | 59,60  |
| HCC                           | 0.040           | Beta(0.15,18.89)                   | 61     |
| Mortality Rates               |                 |                                    |        |
| Other-Cause background mortality| Age/sex specific | Beta(16.44,100.97)                | 25,26  |
| DC-related mortality          | 0.142           | Beta(263.39,353.45)                |        |
| HCC-related mortality         | 0.427           | Beta(57.87,290.73)                 |        |
| LT-related mortality          | 0.116           | Beta(57.87,290.73)                 |        |

(continues)
| Input                                                   | Base case value | Range or probability distribution | Source |
|---------------------------------------------------------|-----------------|-----------------------------------|--------|
| Sustained viral response (SVR)                         |                 |                                   |        |
| EBR/GZR                                                 | 0.991           | Beta(51.09,0.44)                  | 9      |
| peg-IFN/RBV                                             | 0.60            | Beta(4.05,2.7)                    | 23.24  |
| Health state utilities                                 |                 |                                   |        |
| Drug therapy-related multiplier (PEG/RBV)              | 0.85            | Beta(425.48,75.08)                | 62     |
| Drug therapy-related multiplier (no PEG/RBV)           | 1.00            | Gamma(1536.64,0.0)                | Assumption |
| F0–F3                                                   | 0.73/0.86       | Beta(232.95,41.8)                 | 63     |
| Compensated Cirrhosis                                  | 0.69/0.86       | Beta(304.38,75.43)                | 61     |
| DC                                                      | 0.65/0.86       | Beta(375.82,122)                  | 61     |
| HCC                                                     | 0.65/0.86       | Beta(375.82,122)                  | 61     |
| First-year, Post-liver transplant                      | 0.75/0.86       | Beta(197.23,29.19)                | 61     |
| Post-SVR, F0–F3                                        | 0.75/0.86       | Beta(179.37,23.84)                | 61     |
| Post-SVR, F4                                           | 0.76/0.86       | Beta(232.95,41.8)                 | 61     |
| U.S. population norms, men                             |                 |                                   | 64     |
| 20–29 y                                                 | 0.928           | Beta(1057.74,82.07)               |        |
| 30–39 y                                                 | 0.918           | Beta(1178.94,105.31)              |        |
| 40–49 y                                                 | 0.887           | Beta(545.57,69.5)                 |        |
| 50–59 y                                                 | 0.861           | Beta(632.51,102.11)               |        |
| 60–69 y                                                 | 0.84            | Beta(353.26,67.28)                |        |
| 70–79 y                                                 | 0.802           | Beta(398.58,98.4)                 |        |
| 80–89 y                                                 | 0.782           | Beta(417.29,116.33)               |        |
| U.S. population norms, women                           |                 |                                   | 62     |
| 20–29 y                                                 | 0.913           | Beta(1237.29,117.9)               |        |
| 30–39 y                                                 | 0.893           | Beta(1455.96,174.45)              |        |
| 40–49 y                                                 | 0.863           | Beta(626.29,99.42)                |        |
| 50–59 y                                                 | 0.837           | Beta(701.06,136.53)               |        |
| 60–69 y                                                 | 0.811           | Beta(389.02,90.66)                |        |
| 70–79 y                                                 | 0.771           | Beta(426.12,126.57)               |        |
| 80–89 y                                                 | 0.724           | Beta(452.97,172.68)               |        |
| One-time cost ($)                                       |                 |                                   |        |
| Liver transplant                                        | 104 730         | Gamma(61.47,1703.88)              | 12,13  |
| Annual Costs ($)                                        |                 |                                   |        |
| Post-SVR, F0–F4                                         | 0               |                                   |        |
| F0                                                      | 739             | Gamma(61.47,12.03)                | 12,13  |
| F1                                                      | 739             | Gamma(61.47,12.03)                | 12,13  |
| F2                                                      | 749             | Gamma(61.47,12.18)                | 12,13  |
| F3                                                      | 1520            | Gamma(61.47,24.72)                | 12,13  |
| F4                                                      | 1773            | Gamma(61.47,28.84)                | 12,13  |
| DC                                                      | 19 695          | Gamma(61.47,320.43)               | 12,13  |
| HCC                                                     | 36 218          | Gamma(61.47,589.24)               | 12,13  |
| Post-liver transplant                                   | 27 484          | Gamma(61.47,447.15)               | 12,13  |

CKD, chronic kidney disease; CVD, cardiovascular disease; HCV, hepatitis C virus; MI, myocardial infarction; SVR, sustained virologic response; F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma.
3.1 | Base case analysis

Aggregated results are presented for the average cohort irrespective of baseline fibrosis/cirrhosis or CKD status.

3.2 | Subgroup analysis

The results are also provided separately by each fibrosis stage for a typical CKD cohort of patients (eg, average age 55 years, 60% men). The robustness of the results was also tested by changing the baseline demographic characteristics such as sex (ie, proportion of men) and average age.

3.3 | Deterministic sensitivity analysis

We conducted one-way sensitivity analyses for several parameters showing the effect of varying these inputs on the ICUR of EBR/GZR treatment strategies compared with NoTx or peg-IFN/RBV. We varied progression rates, efficacy, unit costs, utility weights, discount rates using the ranges defined in the input tables (Table 1).

3.4 | Probabilistic sensitivity analysis

To quantify the impact of uncertainty in the estimated parameter values (ie, transition probabilities, SVR, costs and utility weights) on the ICUR of EBR/GZR treatment strategies compared with NoTx or peg-IFN/RBV, we performed probabilistic sensitivity analysis (PSA). Using Monte Carlo simulations methods, we drew 1000 random samples from predefined distributions (Table 1).

The parameters of the Gamma and Beta distributions were estimated using the method of moments that relates each parameter to the mean and standard deviation. We used the base case values as estimates of the mean. Standard errors were estimated from confidence intervals or ranges (Supplementary Information).

Results of the PSA were summarized using descriptive statistics and presented using cost-effectiveness acceptability curves (CEAC).32 The CEAC summarizes uncertainty in the results of the cost-effectiveness analysis by showing the probability a regimen is cost-effective as a function of willing-to-pay for a QALY gained.

4 | RESULTS

4.1 | Base case results

Our model predicted that EBR/GZR would significantly reduce the incidence of liver-related complications and prolong life in patients with chronic HCV G1 infection and CKD compared with no treatment or use of peg-IFN/RBV. Compared with NoTx, use of EBR/GZR was projected to reduce the lifetime cumulative incidence of HCC from 23.19% to 0.92% (Table 2). EBR/GZR-based regimens reduced life-time cumulative incidence of DC from 9.45% when peg-IFN/RBV was used to 3.03%. The use of EBR/GZR reduced ESLD mortality to 0.26% from 12.16% with peg-IFN/RBV and 30.40% with NoTx. Compared with NoTx, the use of EBR/GZR was projected to reduce kidney transplants from 2.35% to 1.31% and had little impact on lifetime ESRD mortality.

EBR/GZR-based regimens resulted in higher average remaining QALYs and higher costs compared with NoTx or peg-IFN/RBV. Having an ICUR relative to NoTx that was higher than that of EBR/GZR, peg-IFN/RBV is considered not cost-effective (ie, weakly dominated). The ICUR of EBR/GZR compared with NoTx was $13 201/QALY.

4.2 | Subgroup analysis

The ICUR and ICER of EBR/GZR compared with NoTx were consistently low across baseline fibrosis or cirrhosis status and are lower the more severe the status (Figure 2). Because of the impact of HCV and CKD on quality of life, the ICUR (whose denominator is QALYs) of EBR/GZR compared with NoTx was consistently lower than the

| Outcome/Treatment Regimen | No Treatment | peg-IFN/RBV | EBR/GZR |
|---------------------------|--------------|-------------|---------|
| Decompensated Cirrhosis (%) | 19.28 | 9.45 | 3.03 |
| Hepatocellular Carcinoma (%) | 23.19 | 9.71 | 0.92 |
| Liver Transplant (%) | 1.45 | 0.58 | 0.01 |
| End-stage Liver Disease Mortality (%) | 30.40 | 12.16 | 0.26 |
| Kidney Transplant (%) | 2.35 | 1.72 | 1.31 |
| End-stage Renal Disease Mortality (%) | 12.24 | 12.46 | 12.60 |
| Life Expectancy (y) | 16.98 | 20.59 | 22.94 |
| Discounted QALYs (y) | 8.9199 | 10.2857 | 11.5716 |
| Discounted Costs (Thousands 2015 US$) | 156 236 | 186 701 | 191 242 |
| ICUR ($/QALYs) | — | W. Dominated$ | 13 201 |
| ICER ($/LYs) | — | W. Dominated$ | 5866 |

$W. Dominated, weakly dominated (eliminated through extended dominance because it has an ICER that is greater than that of the more effective regimen of EBR/GZR); ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LYs, life years; QALY, quality-adjusted life years.
ICER (whose denominator is unadjusted life years). Both ICUR and ICER of EBR/GZR compared with NoTx were lower than $100 000 for all CKD1 through CKD4 patients. Treatment of patients with more severe disease with EBR/GZR resulted in higher ICUR and ICER. For example, the highest ICER of EBR/GZR compared with NoTx of $133 900/LYS was for the treatment of patients on HD.

The ICUR varied by age group. For example, ICUR increased from $12 513/QALY to $26 550/QALY when the average at treatment was increased from 20 years to 70 years. The sex of the treated patients had little impact on ICUR or ICER of EBR/GZR compared with NoTx.

4.3 | Deterministic sensitivity analysis

By varying the values of inputs one at a time, we identified the 10 most influential inputs (Figure 3). The ICUR was most sensitive to changes in discount rates, impact of HCV on CKD progression or death, death from HCC and utility following SVR.

4.4 | Probabilistic sensitivity analysis

The results of 1000 Monte Carlo simulations showed that the mean ESLD mortality with the EBR/GZR-based regimen was 0.23% (95% uncertainty intervals, UI: 0.00-1.01) compared with a mean of 10.76% (UI: 3.77-21.61) with peg-INF/RBV and 26.96% (UI: 14.54-26.96) with NoTx.

The CEAC showed that the EBR/GZR-based regimen was cost-effective in 95.3% and in all 1000 simulations at the threshold of $20 000 and $100 000 per QALY, respectively (Figure 4).

5 | DISCUSSION

Treatment of patients with hepatitis C infection and chronic kidney disease (CKD) (especially stages 4–5) with EBR/GZR is safe and highly efficacious. However, the decision to treat HCV in patients with chronic
kidney disease should be based not only on the potential health benefits, but also the risks and costs of EBR/GZR therapy. To evaluate whether use of EBR/GZR provides good value for money spent, we developed a computer-based model of the natural history of chronic HCV genotype 1 infection, CKD and liver disease and projected the associated lifetime costs and quality-adjusted survival. This study showed that use of EBR/GZR was projected to substantially reduce the incidence of liver- and CKD-related complications and mortality in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. Consequently, EBR/GZR-based regimens resulted in higher average remaining costs and survival and were cost-effective at commonly accepted current U.S. standards.33

Renal impairment reduces clearance of PEG/RBV and can enhance treatment-related toxicity. The use of PEG/RBV can also elevate the risk of severe ribavirin-induced anaemia. As a result, not all patients with CKD are eligible or can tolerate PEG/RBV. Our results show that use of EBR/GZR in patients with CKD who are not eligible for treatment with PEG/RBV compared with NoTx had an ICUR of $13 200/QALY and is considered cost-effective.

The results of the subgroup analysis showed that the cost-effectiveness of treatment of patients was more favourable for patients with more severe fibrosis/cirrhosis or less severe CKD disease (Table S1). For example, the lowest and the highest ICUR of EBR/GZR compared with NoTx of $9900 and $217 000/QALY was for the treatment of patients at CKD1 and haemodialysis, respectively. At this high ICUR, treatment of patients on haemodialysis may not be considered cost-effective. However, the overall ICUR of using EBR/GZR to treat an average CKD patient chronically infected with HCV compared with NoTx was well below the accepted threshold for cost-effectiveness.

This study made several simplifying assumptions. First, it excluded the risk of HCC even among patients with advanced fibrosis F3. This has the potential of biasing the results against treatment. Second, the model did not stratify the CKD3, CKD4 and CKD5 states according to albuminuria or proteinuria as was performed in some other models.16,18 Third, because of low utilization in some settings, the model did not consider peritoneal dialysis. For example, only 9% of all incident ESRD cases began renal replacement therapy with peritoneal dialysis in the United States in 2013.2 Inclusion of peritoneal dialysis would
further complicate the model without having any significant impact on the results. Finally, because of the small size of some subgroups (eg, cirrhotic or treatment-experienced patients), we did not use separate efficacy estimates in the subgroup cost-effectiveness analysis.

Despite these limitations, our conclusion regarding the cost-effectiveness of EBR/GZR-based regimens in patients with CKD is robust to variation in many model inputs.

Several other modelling studies of cost-effectiveness of treating chronic hepatitis C patients in the United States have shown that treatment with all-oral direct-acting antivirals is a good use of limited healthcare resources. Although we studied HCV treatment of patients with CKD, a difficult-to-treat population, our results are broadly consistent with those of studies of general HCV patients.

What is unique about this study is that it combined two disease processes (liver and kidney) into one model, something that is very challenging to analyse mathematically. The information provided by this study can be used by payers to guide optimal allocation of limited resources.

In conclusion, our study suggests that use of EBR/GZR has the potential to substantially reduce the incidence of liver- and CKD-related complications and mortality in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease.

The use of EBR/GZR to treat patients with HCV who have CKD is cost-effective in the United States at commonly cited thresholds.

CONFLICT OF INTEREST

Elbasha, Greaves and Nwankwo are current employees of Merck & Co., Inc., Kenilworth, NJ USA and hold restricted share units and/or stock options. Roth has served on advisory boards for Bristol-Myers Squibb and Merck & Co., Inc., Kenilworth, NJ USA.

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