Projected Long-Term Impact of Elbasvir/Grazoprevir (EBR/GZR) Compared to Sofosbuvir Plus Pegylated Interferon/Ribavirin (SOF+PR) in Chronic Hepatitis C Virus Genotype 1 and 4 Patients in Italy: Translation of the C-EDGE Head-to-Head Study Findings

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Objectives

Background

- Hepatitis C virus (HCV) is associated with acute and chronic hepatitis infection[1,2]
  - Approximately 15%-45% of people with acute HCV infection will naturally clear the virus within 6 months; however, the other 55%-85% will go on to develop chronic HCV[1]
  - Chronic HCV infection is one of the leading causes of advanced liver-related diseases (decompensated cirrhosis [DC], hepatocellular carcinoma [HCC]), liver transplant (LT), and liver-related death[2]
  - Chronic HCV infection is usually undiagnosed until decades after infection due to the infection remaining asymptomatic until secondary symptoms start to appear[1]
- One of the leading health problems in Italy is chronic liver disease (CLD), with approximately 10,000 CLD complicated deaths reported every year and over 65% of these caused from HCV infection. Italy has the highest prevalence of HCV and highest death rate for HCC and cirrhosis in Europe[2]
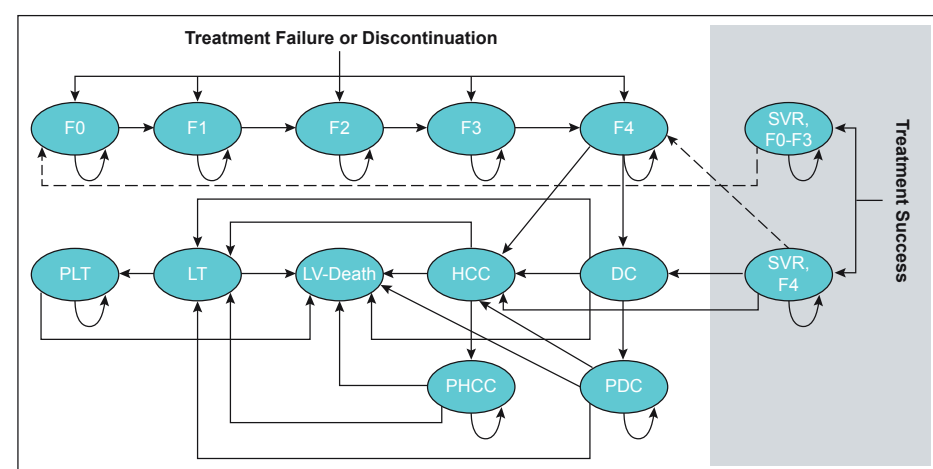
Objective

- The C-EDGE Head-to-Head study was a phase III, open-label clinical trial that assessed the efficacy and safety of elbasvir/grazoprevir (EBR/GZR) versus sofosbuvir plus pegylated interferon/ribavirin (SOF+PR) in 257 treatment-naïve and PR prior treatment-failure subjects with chronic HCV genotype 1 (G1) or 4 (G4) infection[3]
- The aim of this analysis was to translate short-term findings from the study into long-term predictions of the impact of EBR/GZR compared to SOF+PR on the incidence of liver-related morbidity and mortality in Italy

Methods

- A Markov model was created to simulate the natural history of chronic HCV and estimate the lifetime cumulative incidence of advanced liver-related diseases, DC, HCC, LT, and liver-related death. The structure of the model is based on other published HCV economic models and consists of 18 health states (see **Figure 1**). Patients enter the model in the health state based on the severity of chronic HCV described by the degree of fibrosis using the METAVIR scoring system F0 to F4. F0 to F3 are defined as noncirrhotic and F4 is defined as cirrhotic. The model assumes that a person with a given fibrosis score may progress to more severe stages of liver disease or may remain in that health state. In the absence of successful treatment, regression to less severe health states is not permitted. However, after a successful treatment, a person can achieve sustained virologic response (SVR), which is considered a cure for HCV in patients who are noncirrhotic

Table 1: SVR 12 rates used in the model from the C-EDGE Head-to-Head trial[3]

| Treatment	Overall Population	Genotype 1	Genotype 4
EBR/GZR	99.2% (128/129)	99.2% (122/123)	100% (6/6)
SOF+PR	90.5% (114/126)	91.7% (111/121)	60.0% (3/5)

Table 2: Natural history transition probabilities

Health State, From	Health State, To	Transition Probability (per year)	Source
F0	F1	0.117	Thein et al[5]
F1	F2	0.085	
F2	F3	0.120	
F3	F4	0.116	
F4	DC	0.029	Fattovich et al[6]
	HCC	0.028	
F4 SVR	DC	0.008	Van der Meer et al[7]; Cardoso et al[8]
	HCC	0.002	
	F3 SVR	0.086	D'Ambrosio et al[9]
	F4	0.014	OHTN[10]; Aspinall et al[11]
DC	HCC	0.068	Planas et al[12]
	LT	0.016	
	LVD	0.140	Planas et al[12]
	LT	0.008	
HCC	LVD	0.427	Fattovich et al[6]
PDC	LVD	0.103	Planas et al[12]
LT	LVD	0.166	Wolfe et al[13]
PLT	LVD	0.044	Wolfe et al[13]
SVR	F0	0.014	OHTN[10]; Aspinall et al[11]

Key: DC=first-year decompensated cirrhosis; F0=no fibrosis; F1=portal fibrosis without septa; F2=portal fibrosis with few septa; F3=portal fibrosis with numerous septa without cirrhosis; F4=compensated cirrhosis; HCC=first-year hepatocellular carcinoma; LT=first-year liver transplant; LVD=liver-related death; PDC=subsequent years decompensated cirrhosis states; PHCC=subsequent years hepatocellular carcinoma states; PLT=subsequent years liver transplant; SVR=sustained virologic response.

Figure 1: Model structure

Key: DC=first-year decompensated cirrhosis; F0=no fibrosis; F1=portal fibrosis without septa; F2=portal fibrosis with few septa; F3=portal fibrosis with numerous septa without cirrhosis; F4=compensated cirrhosis; HCC=first-year hepatocellular carcinoma; LT=first-year liver transplant; LVD=liver-related death; PDC=subsequent years decompensated cirrhosis states; PHCC=subsequent years hepatocellular carcinoma states; PLT=subsequent years liver transplant; SVR=sustained virologic response.

- Efficacy for both regimens was obtained from the C-EDGE Head-to-Head trial. **Table 1** reports the proportion of overall, G1, and G4 patients achieving SVR 12 weeks after the completion of treatment in the EBR/GZR groups and in the SOF+PR groups. The proportion of patients who discontinued treatment was 0.0% (0/129) and 0.8% (1/126) for EBR/GZR and SOF+PR, respectively
- Natural history annual transition probabilities shown in **Table 2** were sourced from published studies. Baseline patient characteristics were obtained from the Italian PITER-HCV cohort study,[2] including distribution of METAVIR fibrosis stage at baseline, mean age, and proportions of males/females. The proportions of patients who are G1 and G4 are based on the reported HCV prevalence/infected population from a literature search by Gower et al, 2014,[4] and were 94.5% and 5.5%, respectively. Life table for the Italian general population was used to model nonliver-related deaths

Results

- EBR/GZR was projected to reduce lifetime (30 years) cumulative incidence of DC by 18.93%, 17.66%, and 52.32% for overall patients and in G1 and G4, respectively, compared with SOF+PR
- The incidence of HCC was also projected to reduce by 29.40%, 27.60%, and 66.57% for overall patients and in G1 and G4, respectively, when comparing EBR/GZR against SOF+PR. As a result, EBR/GZR was projected to reduce liver-related mortality by 25.83% in the overall population and 24.19% and 62.32% for G1 and G4 populations, respectively, compared with SOF+PR
- Detailed results are presented in **Table 3**. EBR/GZR was estimated to extend life expectancy by 0.58 years in the overall population compared to SOF+PR and by 0.54 and 2.68 years in the G1 and G4 populations, respectively
- **Figure 2** shows the cumulative incidence of DC, HCC, LT, and liver-related mortality for EBR/GZR and SOF+PR over the 30-year period. For example, within the first 5 years, EBR/GZR was projected to reduce the incidence of DC by 23.15% overall and 21.65% and 58.5% for G1 and G4 populations, respectively, compared to SOF+PR. The reduction for cumulative incidence of DC increases over time. Similar results are also shown for HCC, LT, and liver-related mortality incidence rates

Table 3: Reduction in liver-related morbidity and mortality in HCV G1 and G4 populations for EBR/GZR compared to SOF+PR in Italy (over 30 years)

	Decompensated Cirrhosis (cumulative incidence)	Hepatocellular Carcinoma (cumulative incidence)	Liver Transplant (cumulative incidence)	Liver Disease Mortality (cumulative incidence)	Life Expectancy (undiscounted life years)
Overall population					
EBR/GZR	0.098	0.079	0.008	0.123	21.441
SOF+PR	0.121	0.112	0.010	0.166	20.858
% change (EBR/GZR vs SOF+PR)	-18.93%	-29.40%	-21.18%	-25.83%	2.80%
Genotype 1					
EBR/GZR	0.099	0.079	0.008	0.124	21.433
SOF+PR	0.120	0.110	0.010	0.163	20.895
% change (EBR/GZR vs SOF+PR)	-17.66%	-27.60%	-19.78%	-24.19%	2.57%
Genotype 4					
EBR/GZR	0.096	0.076	0.008	0.119	21.495
SOF+PR	0.201	0.227	0.018	0.316	18.812
% change (EBR/GZR vs SOF+PR)	-52.33%	-66.57%	-55.88%	-62.32%	14.26%

Figure 2: Cumulative incidence of liver-related morbidities and mortality in HCV G1 and G4 populations for EBR/GZR compared to SOF+PR in Italy
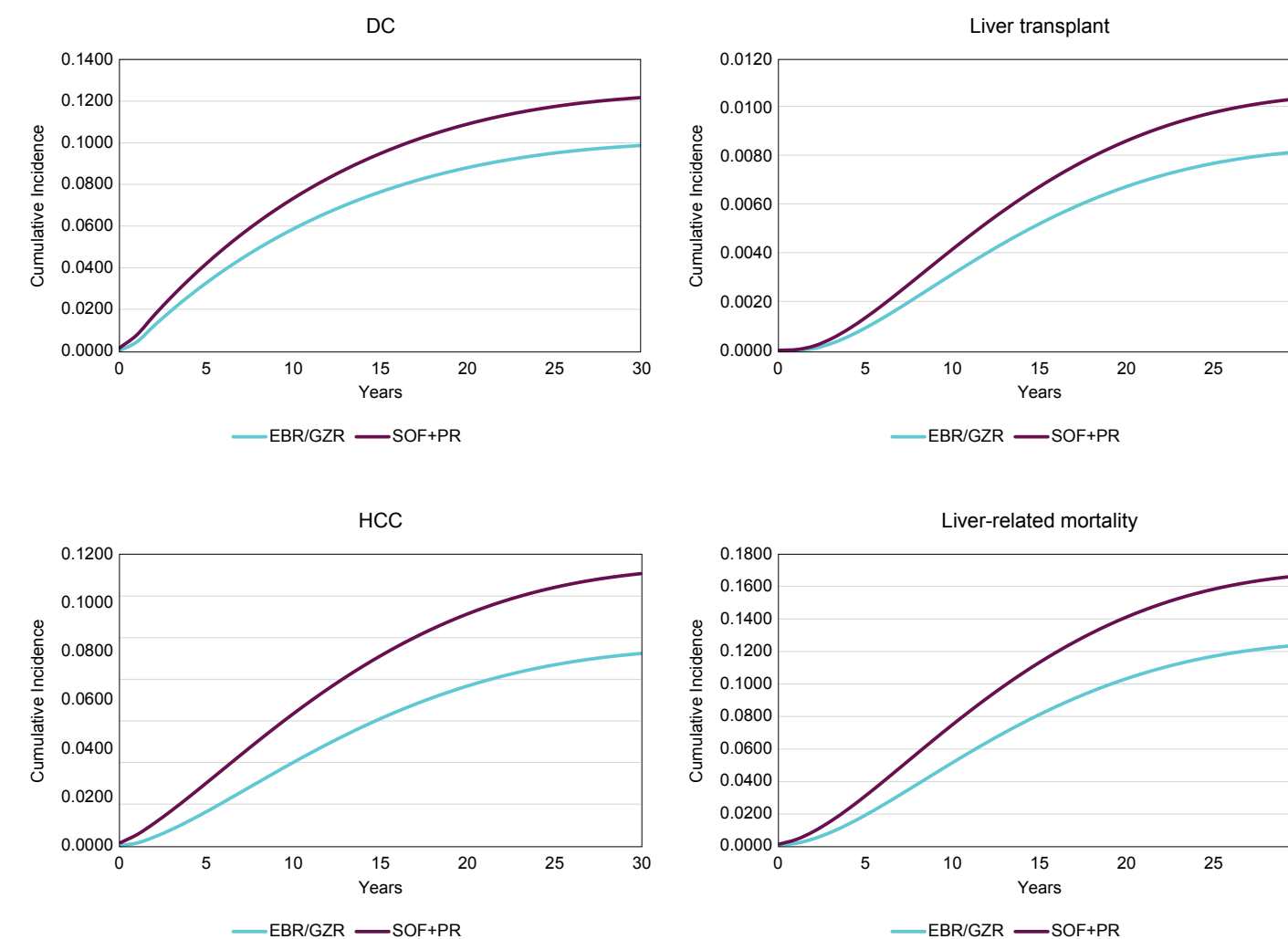
- **Sensitivity analysis**: The results were sensitive to assumed baseline patient characteristics including the distribution of baseline fibrosis scores. These impact the efficacy of the treatments, the rate of disease progression, and mortality rate. The main limitation of the data was the small number of patients who were G4 in the C-EDGE trial; 6 patients (4.7%) and 5 patients (4%) were G4 in the EBR/GZR arm and SOF+PR arm, respectively

Conclusions

Based on the efficacy data from the C-EDGE Head-to-Head study and a natural history model for HCV, EBR/GZR was projected to substantially reduce the cumulative incidence of liver-related complications and liver-related mortality in patients with HCV G1 and G4 infection when compared with SOF+PR in Italy. EBR/GZR was also shown to increase life expectancy for HCV G1 and G4 patients when compared with SOF+PR.

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