High Efficacy in Patients With Chronic Hepatitis C Virus (HCV) Genotype 1b Infection Treated with Elbasvir/ Grazoprevir for 12 Weeks: An Integrated Analysis

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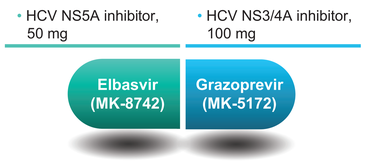
Background

- Genotype (GT)1b is the most common subtype of hepatitis C virus (HCV) infection, responsible for 22% of all infections worldwide[1]
  - Significant regional variability
    - 26% of cases in North America
    - 39% of cases in Latin America
    - 50% of cases in Europe
  - Common in many countries throughout Asia
    - 65% of infections in Japan
    - 45% of infections in Taiwan and South Korea
- Elbasvir (EBR) is a once-daily NS5A inhibitor and grazoprevir (GZR) is a once-daily HCV NS3/4A protease inhibitor (**Figure 1**)
  - Approved in Europe, the United States, Canada, and other countries worldwide[2]
  - Broad activity vs most HCV genotypes in vitro[3-5]
  - Efficacious in treatment-naive and treatment-experienced patients, cirrhotic and noncirrhotic patients, HIV/HCV co-infected patients, and those with chronic kidney disease[6-9]

Figure 1. EBR/GZR



- Initial phase 2 study demonstrated
  - 100% (13/13) of GT1b-infected patients treated for 12 weeks achieved SVR12[10]
  - 93.5% (29/31) of GT1b-infected patients treated for 8 weeks achieved SVR12[11]
- Subsequently, phase 2/3 studies demonstrated an SVR12 of 96.5% (246/255) in GT1b-infected patients treated for 12 weeks
  - Excluding 7 patients with nonvirologic failure, 99.2% (246/248) achieved SVR12
  - Virologic failure (relapse) occurred in 0.8% (2/255) of patients

Aim

- To perform an integrated analysis of 1070 patients with HCV GT1b infection from 30 countries who received EBR/GZR for 12 weeks in 11 phase 2/3 international clinical trials

Patients and Methods

Study Design

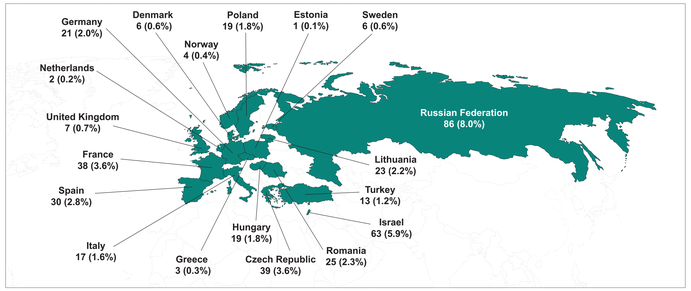
- Retrospective integrated post hoc analysis of data from 11 clinical trials in the EBR/GZR phase 2/3 clinical development program, using a pooled dataset of 1070 patients who received EBR/GZR (50 mg/100 mg) for 12 weeks
- Patients were treatment-naive or treatment-experienced, and included those with compensated cirrhosis or HIV co-infection
  - Patients with decompensated liver disease or evidence of hepatocellular carcinoma were excluded
- The primary endpoint of all 11 studies was SVR12 (HCV RNA <15 IU/mL in phase 3 studies and <25 IU/mL in phase 2 studies)
  - Full analysis set (FAS): includes all patients who received ≥1 dose of study medication
  - Modified FAS (mFAS): excludes patients with nonvirologic failure
- Population sequencing was performed at baseline and at the time of virologic failure.
  - The specific NS5A loci evaluated were any polymorphism at amino acid positions 28, 30, 31, and 93

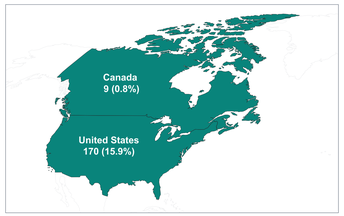
Results

Demographics and Characteristics

- Patients from 30 countries were enrolled (**Figure 2** and **Table 1**)
  - 508 patients (47.5%) from Asian countries
    - Japan was the most heavily represented country, contributing 26.9% of all enrolled patients
  - 359 patients (34%) from European countries
  - 180 patients (17%) from the American continent
  - 23 patients (2%) from Australasia

Figure 2. Geographic distribution of enrolled patients





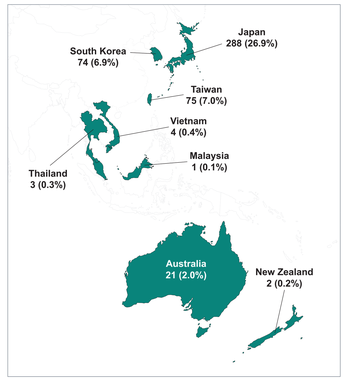


Table 1. Patient demographics

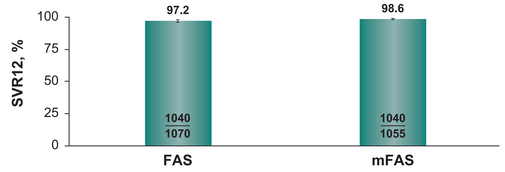
	All patients (N = 1070)
Female, n (%)	534 (49.9)
Race, n (%)	
Asian	462 (43.2)
Black/African American	95 (8.9)
White	504 (47.1)
Other/missing	9 (0.8)
Age, years, mean (SD)	53.7 (13.0)
Treatment history, n (%)	
Naive	851 (79.5)
Experienced	219 (20.5)
Baseline viral load, n (%)	
≤800,000 IU/mL	342 (32.0)
>800,000 IU/mL	728 (68.0)
HIV co-infection, n (%)	54 (5.1)
Cirrhotic, n (%)	189 (17.7)

SD, standard deviation.

Virologic Response

- In the FAS population, 97.2% (1040/1070) of patients with HCV GT1b infection receiving EBR/GZR for 12 weeks achieved SVR12 (**Figure 3**)
  - SVR12 in the mFAS population was 98.6% (1040/1055)

Figure 3. SVR12

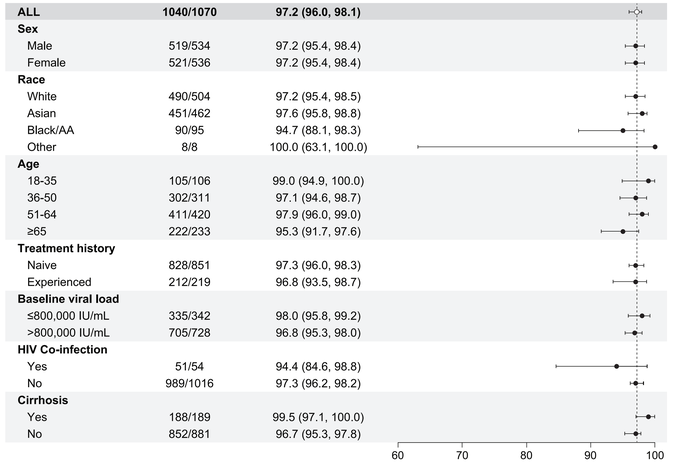


	FAS	mFAS
Virologic failure: relapse	15	15
Nonvirologic failure	15	0

FAS includes all patients who received ≥1 dose of study medication. mFAS excludes 15 patients who discontinued for reasons unrelated to study medication.

- Subgroup analyses are shown in **Figure 4**

Figure 4. SVR12 subgroup analyses (FAS)

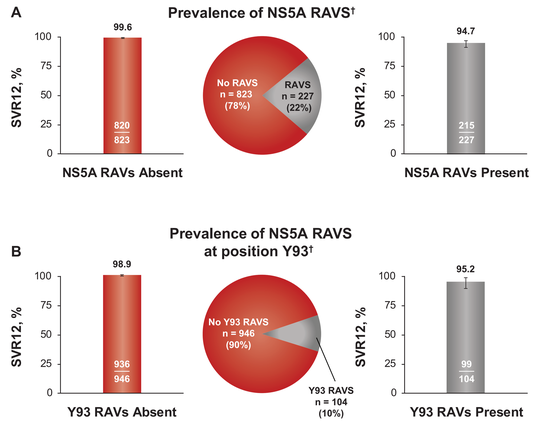


ALL	**1040/1070**	**97.2 (96.0, 98.1)**
Sex		
Male	519/534	97.2 (95.4, 98.4)
Female	521/536	97.2 (95.4, 98.4)
Race		
White	490/504	97.2 (95.4, 98.5)
Asian	451/462	97.6 (95.8, 98.8)
Black/AA	90/95	94.7 (88.1, 98.3)
Other	8/8	100.0 (63.1, 100.0)
Age		
18-35	105/106	99.0 (94.9, 100.0)
36-50	302/311	97.1 (94.6, 98.7)
51-64	411/420	97.9 (96.0, 99.0)
≥65	222/233	95.3 (91.7, 97.6)
Treatment history		
Naive	828/851	97.3 (96.0, 98.3)
Experienced	212/219	96.8 (93.5, 98.7)
Baseline viral load		
≤800,000 IU/mL	335/342	98.0 (95.8, 99.2)
>800,000 IU/mL	705/728	96.8 (95.3, 98.0)
HIV Co-infection		
Yes	51/54	94.4 (84.6, 98.8)
No	989/1016	97.3 (96.2, 98.2)
Cirrhosis		
Yes	188/189	99.5 (97.1, 100.0)
No	852/881	96.7 (95.3, 97.8)

AA, African American; CI, confidence interval.

- NS5A resistance-associated variants (RAVs) at amino acid positions 28, 30, 31, and 93 were detected in 21.6% (227/1050) of patients at baseline **(Figure 5A)**
  - SVR12 was 94.7% (215/227) and 99.6% (820/823) in patients with and without baseline NS5A RAVs, respectively
- Polymorphisms at amino acid Y93 were present at baseline in 9.9% (104/1050) of patients (**Figure 5B**)
  - Of the 104 patients with Y93 polymorphisms at baseline, only 3 did not have a Y93H variant (Y93C/Y, n = 1; Y93S, n = 2).
  - SVR12 was 95.2% (99/104) in patients with polymorphisms at Y93
    - All 5 patients with a Y93 polymorphism at baseline who subsequently had virologic failure had the Y93H variant

Figure 5. Prevalence and impact on SVR12 of baseline NS5A RAVs at (A) positions 28, 30, 31, and 93 and (B) at position 93 only in patients with HCV GT1b infection†



†Resistance analysis population includes 1050 patients with HCV GT1b infection, baseline sequencing available, and a treatment outcome of either SVR12 or virologic failure.

Safety

- A 12-week regimen of EBR/GZR was well tolerated, with a favorable safety profile in patients with HCV GT1b infection included in this analysis
- Serious adverse events (SAEs) occurred in 3.3% (35/1070) of patients, comparable to the rate of 2.9% (3/105) observed in placebo controls
- Specifically, late elevations of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) (elevation of ALT or AST >5× upper limit of normal on or after treatment week 4 after normalization on treatment), were rare and observed in 1.1% of GT1b-infected patients, which was comparable to the rate of 0.8% in the overall population of patients treated with EBR/GZR for 12 weeks

Conclusions

- This integrated analysis of 1070 patients demonstrated EBR/GZR for 12 weeks was highly efficacious in patients with HCV GT1b infection.
- The overall SVR12 was 97.2% (FAS population)
  - SVR12 was 98.6% in the mFAS population, which excluded patients with nonvirologic failure
  - SVR12 rates were high regardless of race, age, treatment history, baseline viral load, presence of cirrhosis, HIV co-infection, or presence of baseline NS5A RAVs
- EBR/GZR demonstrated a favorable safety profile
  - The rates of SAEs were comparable between those treated with EBR/GZR or placebo
  - Late ALT/AST elevations were detected in 1.1% of patients, comparable to the rate in the overall population of all patients treated with EBR/GZR for 12 weeks
- Further investigation of shorter duration regimens for GT1b-infected patients is warranted
  - SVR12 rates of 93.5% (29/31) were achieved in noncirrhotic patients with GT1b infection receiving EBR/GZR for 8 weeks
  - An 8-week treatment duration for EBR/GZR is approved in Canada for treatment-naive, noncirrhotic GT1b-infected patients

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