Poster #851

# Final Results From Phase 3 Portion in Phase 2/3 Study of Elbasvir/Grazoprevir in Hepatitis C Genotype 1-Infected Japanese Patients

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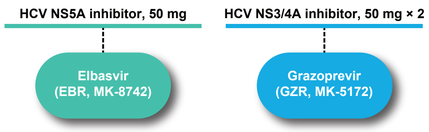
## Background

**Figure 1. EBR + GZR**




- Broad activity versus most hepatitis C virus (HCV) genotypes in vitro[1-3]
- Retains in vitro activity against many clinically relevant resistance-associated variants (RAVs)[1-3]
- Efficacious in treatment-naïve and treatment-experienced cirrhotic and noncirrhotic patients with HCV, in HIV/HCV coinfected patients, and chronic kidney disease (CKD) stage 4/5 patients with HCV[4-8]
- All-oral, once-daily regimen
- Received approval as ZEPATIER™ for the treatment of chronic hepatitis C (CHC) genotypes 1 or 4 infection in US and EU

1. Summa V, et al. *Antimicrobial Agent Chemother.* 2012;56:4161-4167.
2. Coburn CA, et al. *Chem Med Chem.* 2013;8(12):1930-1940.
3. Harper S, et al. *ACS Med Chem Lett.* 2012;3(4):332-336.
4. Zeuzem S, et al. *Ann Intern Med.* 2015;163(1):1-13.
5. Lawitz E, et al. *Lancet.* 2015;385(9973):1075-1086.
6. Rockstroh J, et al. *Lancet HIV.* 2015;2(8):e319-e327.
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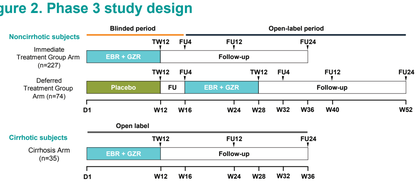
8. Roth D, et al. *Lancet.* 2015;386(10003):1537-1545.

## Aim

- The study was conducted as a Phase 2/3 design. The dose of grazoprevir (GZR) (100 mg) was selected based on the results of the Phase 2 portion of the study
- The aim of the Phase 3 portion of the Phase 2/3 study was to evaluate the efficacy and safety of this drug combination in genotype 1 (GT1)-infected treatment-naïve or IFN-experienced Japanese chronic hepatitis C (CHC) patients with or without cirrhosis
  - In this report, we present SVR12 (sustained virologic response 12 weeks after completion of therapy) in the immediate-treatment group (ITG) arm, the deferred-treatment group (DTG) arm, and compensated cirrhosis arm
  - Also, we present SVR24 data from all 3 arms

## Methods

**Figure 2. Phase 3 study design**




EBR: elbasvir; GZR: grazoprevir.

- Phase 3, randomized, placebo-controlled, multisite, double-blind study
  - CHC patients without cirrhosis were randomized in a 3:1 ratio to the ITG arm or DTG arm and received elbasvir (EBR) 50 mg + GZR 100 mg QD or placebo for 12 weeks
  - After a 4-week follow-up, each patient was unblinded and placebo recipients received open-label EBR + GZR
  - CHC patients with compensated cirrhosis received open-label EBR + GZR for 12 weeks

## Methods (continued)

**Key inclusion criteria**

- GT1-infected Japanese CHC subject
- Without cirrhosis or with compensated cirrhosis
- 20-80 years of age; male and female
- Treatment naïve or treatment experienced for interferon-based therapy without direct-acting antivirals
- HCV RNA at the time of screening: ≥5.0 log IU/mL

**Key exclusion criteria**

- Coinfection with hepatitis B virus or HIV
- Creatinine clearance is less than 50 mL/min

**Key endpoints**

- Efficacy (full analysis set [FAS])
- Primary endpoint: SVR12 (HCV RNA <15 IU/mL at follow-up week 12 [Roche COBAS TaqMan HCV assay, ver.2.0])
- Secondary endpoint: SVR24
- Exploratory endpoint: prevalence and impact of baseline NS3 and NS5A RAVs on SVR12
- Safety (all subjects as treated [ASaT])
- All data collected from the first study medication to FU4
- Adverse events (AEs)
- Laboratory abnormalities

## Results

**Table 1. Demographics**

| Factors | | Noncirrhotic: EBR + GZR (Immediate) | Noncirrhotic: Placebo (Deferred) | Cirrhotic: EBR + GZR |
|---|---|---|---|---|
| **Total** | | 227 | 74* | 35 |
| **Gender** | Male, n : Female, n | 87 : 140 | 21 : 53 | 18 : 17 |
| **Age** | Median years (range) | 63 (21-80) | 63 (34-80) | 65 (43-79) |
| | <65, n (%) | 123 (54%) | 40 (54%) | 16 (46%) |
| | ≥65, n (%) | 104 (46%) | 34 (46%) | 19 (54%) |
| **HCV subtype, n (%)** | GT1a | 4 (2%) | 1 (1%) | 1 (3%) |
| | GT1b | 223 (98%) | 73 (99%) | 34 (97%) |
| **Prior treatment, n (%)** | Naïve | 149 (66%) | 49 (66%) | 20 (57%) |
| | Intolerant to prior P/R | 11 (5%) | 3 (4%) | 3 (9%) |
| | Relapse to prior P/R | 40 (18%) | 13 (18%) | 6 (17%) |
| | Nonresponse to prior P/R | 27 (12%) | 9 (12%) | 6 (17%) |
| **IL28B, n (%) (rs12979860)** | Major (CC) | 131 (58%) | 44 (60%) | 22 (63%) |
| | Minor (TC) | 86 (38%) | 29 (39%) | 13 (37%) |
| | Minor (TT) | 10 (4%) | 1 (1%) | 0 (0%) |
| **Baseline HCV RNA, median log IU/mL (range)** | | 6.3 (4.7-7.2) | 6.3 (4.8-7.3) | 6.4 (5.1-7.1) |

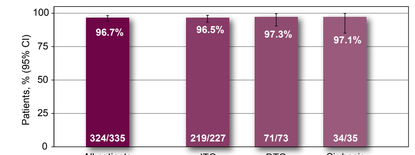
*73 received the deferred active treatment, as 1 subject discontinued the study during the initial treatment period.

## Results (continued)

**Virologic response**

- Overall SVR12 was 96.7% in the combined ITG, DTG, and cirrhosis population receiving EBR/GZR for 12 weeks (**Figure 3**)
  - 7/335 (2.1%) virologic failures (relapse)
- Overall SVR24 was 96.4% (**Figure 4**)
  - One patient relapsed between follow-up weeks 12 and 24

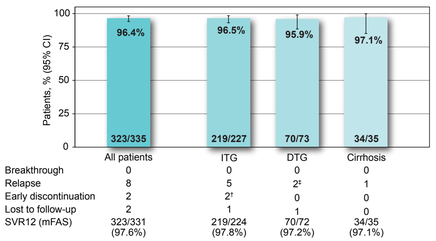
**Figure 3. SVR12 (FAS)**




| | All patients | ITG | DTG | Cirrhosis |
|---|---|---|---|---|
| Breakthrough | 0 | 0 | 0 | 0 |
| Relapse | 7 | 5 | 1 | 1 |
| Early discontinuation | 2 | 2† | 0 | 0 |
| Lost to follow-up | 2 | 1 | 1 | 0 |
| SVR12 (mFAS) | 324/331 (97.9%) | 219/224 (97.8%) | 71/72 (98.6%) | 34/35 (97.1%) |

†Discontinued due to serious AEs (cardiac sarcoidosis and cerebral infarction).
ITG: immediate treatment group arm; DTG: active treatment period in deferred treatment group arm.
FAS includes all patients who received ≥1 dose of study medication; modified FAS (mFAS) excludes patients who discontinued early and/or patient who was lost to follow-up.

**Figure 4. SVR24 (FAS)**



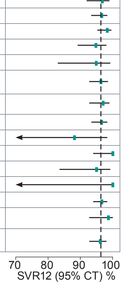

| | All patients | ITG | DTG | Cirrhosis |
|---|---|---|---|---|
| Breakthrough | 0 | 0 | 0 | 0 |
| Relapse | 8 | 5 | 2‡ | 1 |
| Early discontinuation | 2 | 2† | 0 | 0 |
| Lost to follow-up | 2 | 1 | 1 | 0 |
| SVR12 (mFAS) | 323/331 (97.6%) | 219/224 (97.8%) | 70/72 (97.2%) | 34/35 (97.1%) |

†Discontinued due to serious AEs (cardiac sarcoidosis and cerebral infarction).
‡One patient relapsed just after FU12; detected HCV RNA <15 IU/mL at FU12 and confirmed HCV RNA positive 2 weeks after.
ITG: immediate treatment group arm; DTG: active treatment period in deferred treatment group arm.
FAS includes all patients who received ≥1 dose of study medication; mFAS excludes patients who discontinued early and/or patient who was lost to follow-up.

- Subgroup analysis is shown in **Figure 5**

**Figure 5. SVR12 subgroup analysis (FAS)**

| Subgroup | | Patients, n/N | SVR12 (95% CI), % |
|---|---|---|---|
| **Total** | | 324/335 | 96.7 (94.2-98.3) |
| **Gender** | Male | 121/125 | 96.8 (92.0-99.1) |
| | Female | 203/210 | 96.7 (93.3-98.6) |
| **Age** | <65 y | 176/179 | 98.3 (95.2-99.7) |
| | ≥65 y, <75 y | 110/116 | 94.8 (89.1-98.1) |
| | ≥75 y | 38/40 | 95.0 (83.1-99.4) |
| **IL28B genotype (rs12979860)** | Major | 190/197 | 96.4 (92.8-98.6) |
| | Minor | 134/138 | 97.1 (92.7-99.2) |
| **Prior treatment** | Naïve | 211/218 | 96.8 (93.5-98.7) |
| | Intolerant | 15/17 | 88.2 (63.6-98.5) |
| | Relapse | 59/59 | 100 (93.9-100) |
| | Nonresponse | 39/41 | 95.1 (83.5-99.4) |
| **HCV genotype** | 1a | 6/6 | 100 (54.1-100) |
| | 1b | 318/329 | 96.7 (94.1-98.3) |
| **Baseline HCV RNA (IU/mL)** | ≤800,000 | 75/76 | 98.7 (92.9-100) |
| | >800,000 | 249/259 | 96.1 (93.0-98.1) |




- The prevalence of baseline NS3 RAVs† was 1.8% (6/331). There was no impact of baseline NS3 RAVs to SVR12 rates

†NS3 RAVs: any variants at positions 155, 156, and 168 detected by population sequencing (sensitivity threshold: 25%).

- The prevalence of baseline NS5A RAVs was 29.6% (98/331). SVR12 rates in GT1 subjects without or with baseline NS5A RAVs were 99.1% (231/233) or 94.9% (93/98), respectively. Regardless of presence of baseline NS5A RAVs, the SVR12 in GT1b subjects still exceeded 94% (**Table 2**)

**Table 2. Impact of NS5A RAVs‡ at baseline**

| Population | SVR12 (%): Overall Efficacy in Subjects With Sequence | SVR12 (%): NS5A RAVs Not Detected | SVR12 (%): NS5A RAVs Detected |
|---|---|---|---|
| Overall | 324/331† (97.7%) | 231/233† (99.1%) | 93/98† (94.9%) |
| By genotype and subtype | | | |
| GT1a | 6/6 (100.0%) | 4/4 (100.0%) | 2/2 (100.0%) |
| GT1b | 318/325 (97.8%) | 227/229 (99.1%) | 91/96 (94.8%) |

SVR12 (%) = number of subjects achieving SVR12/total number of subjects, with RAVs selected in each category.
†Resistance analysis population: patients who achieved SVR12 or who met virologic failure criteria.
‡NS5A RAVs: any variant at positions 28, 30, 31, and 93 detected by population sequencing (sensitivity threshold: 25%).

**Safety**

- The frequency and nature of AEs were similar in patients receiving EBR/GZR (ITG + DTG, ITG or cirrhosis) and placebo (**Table 3**)
  - Drug-related AEs were slightly more frequent on EBR/GZR

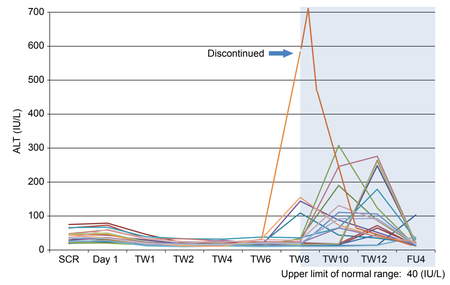
**Table 3. Adverse events (≥5%) through FU4 (ASaT)**

| | Noncirrhotic: EBR + GZR (ITG + DTG) | | Noncirrhotic: EBR + GZR (ITG) | | Noncirrhotic: Placebo (DTG) | | Cirrhotic: EBR + GZR | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 300 | | 227 | | 74 | | 35 | |
| With one or more AEs | 195 | (65.0) | 147 | (64.8) | 50 | (67.6) | 28 | (80.0) |
| With drug-related† AEs | 77 | (25.7) | 58 | (25.6) | 14 | (18.9) | 13 | (37.1) |
| With serious AEs | 12 | (4.0) | 11 | (4.8) | 1 | (1.4) | 0 | (0.0) |
| With drug-related† serious AEs | 2 | (0.7) | 2 | (0.9) | 0 | (0.0) | 0 | (0.0) |
| Nasopharyngitis | 47 | (15.7) | 34 | (15.0) | 12 | (16.2) | 5 | (14.3) |
| Alanine aminotransferase increased | 16 | (5.3) | 13 | (5.7) | 1 | (1.4) | 5 | (14.3) |
| Aspartate aminotransferase increased | 14 | (4.7) | 11 | (4.8) | 2 | (2.7) | 5 | (14.3) |
| Diarrhea | 15 | (5.0) | 11 | (4.8) | 2 | (2.7) | 3 | (8.6) |
| Constipation | 12 | (4.0) | 8 | (3.5) | 3 | (4.1) | 3 | (8.6) |
| Headache | 12 | (4.0) | 10 | (4.4) | 1 | (1.4) | 2 | (5.7) |
| Rash | 9 | (3.0) | 9 | (4.0) | 1 | (1.4) | 3 | (8.6) |
| Malaise | 11 | (3.7) | 7 | (3.1) | 3 | (4.1) | 2 | (5.7) |
| Blood creatine phosphokinase increased | 9 | (3.0) | 6 | (2.6) | 4 | (5.4) | 1 | (2.9) |
| Anemia | 2 | (0.7) | 1 | (0.4) | 0 | (0.0) | 2 | (5.7) |

Every subject is counted a single time for each applicable row and column.
A specific AE appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
†Determined by investigator to be related to the drug.

- 6.0% (20/335) of patients receiving EBR/GZR had drug-related liver transaminase elevation (**Figure 6**), including approximately 1.8% (6/335) with late liver transaminase elevation (>5×ULN) after initially normalizing on treatment
- Late ALT/AST elevation events were generally detected at TW8 and transient. Five of 6 patients recovered during continued administration of EBR/GZR; the remaining patient recovered after withdrawal of study drug
- No symptoms such as gastrointestinal disorders or rash developed; no abnormalities in bilirubin total, eosinophil counts, or INR accompanied by late ALT/AST elevation were noted
- All patients who experienced ALT elevation reached SVR24

**Figure 6. ALT transition up to FU4 in 20 patients with drug-related ALT elevation**




## Conclusion

- SVR12 and SVR24 was achieved by over 96% of patients
  - High efficacy for GT1-infected Japanese CHC patients
  - High efficacy also in compensated cirrhosis
  - No on-treatment virologic failures occurred
  - Baseline NS3 and NS5A RAVs had no clinically remarkable impact on the efficacy
- EBR/GZR was largely safe and well tolerated
  - Low rates of AEs; comparable to placebo
  - Low rates of late ALT/AST elevations; the events were transient and reversible, no symptoms developed, no other accompanying liver function test abnormalities
- Coadminstration of EBR/GZR is an important treatment option in GT1-infected HCV patients, including patients with compensated cirrhosis

**Disclosures**

- Fumitaka Suzuki - Speaking and Teaching: BMS
- Yoshiyasu Karino - Speaking and Teaching: BMS K.K.
- Kazuaki Chayama - Advisory Committees or Review Panels: Mitsubishi Tanabe, Taisho Toyama; Consulting: AbbVie; Grant/Research Support: Ajinomoto, AbbVie, Aska, Astellas, Bristol Squibb, Daiichi Sankyo, Sumitomo Dainippon, Eisai, GlaxoSmithKline, Mitsubishi Tanabe, Nippon Kayaku, Otsuka, Sogo Rinsho Médéfi, Taiho, Takeda, Toray, Torii, Tsumura, Zeria; Speaking and Teaching: Abbott, AbbVie, Ajinomoto, Astellas, AstraZeneca, Bayer, Bristol Squibb, Chugai, Sumitomo Dainippon, Eidia, Eisai, Gilead, GlaxoSmithKline, JIMRO, Johnson & Johnson, Mitsubishi Tanabe
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- Michael Robertson - Employment: Merck; Stock Shareholder: Merck
- Stuart Black - Employment: Merck
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