Efficacy and Safety of Elbasvir/Grazoprevir in Treatment-Naive Participants With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection (C-CORAL): A Phase 3 Randomized, International Trial

Presented at
The International Liver Congress™ 2017;
April 19-23, 2017;
Amsterdam, The Netherlands

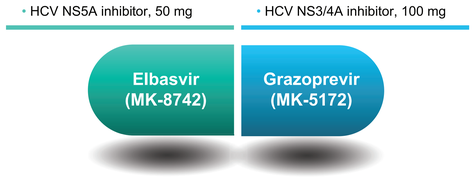
Wei L[1]*; Zhdanov K[2]*; Burnevich E[3]; Sheen I-S[4]; Heo J[5]; Nguyen VK[6]; Tanwandee T[7]; Cheng P-N[8]; Kim DY[9]; Tak WY[10]; Kizhlo S[11]; Duan Z[12]; Peng C-Y[13]; Liang LW[14]; Evans B[14]; Hanna G[14]; Barr E[14]; Robertson M[14]; Ingravallo P[14]; Talwani R[14]; George J[15]
*Co-first authors contributed equally to this poster

[1]Peking University People's Hospital, Beijing, China; [2]Military Medical Academy n.a. S.M. Kirov, St. Petersburg, Russia; [3]Moscow Sechenov Medical Academy, Moscow, Russia; [4]Linkou Medical Center, Chang Gung Memorial Hospital, Taipei Taiwan; [5]Pusan National University Hospital, Pusan, South Korea; [6]National Hospital of Tropical Diseases, Hanoi, Vietnam; [7]Siriraj Hospital, Bangkok, Thailand; [8]National Cheng Kung University Hospital, Tainan, Taiwan; [9]Severance Hospital, Seoul, South Korea; [10]Kyungpook National University Hospital, Daegu, South Korea; [11]City Center for AIDS and Infectious Diseases Treatment and Prophylaxis, St. Petersburg, Russia; [12]Beijing Youan Hospital, Capital Medical University, Beijing, China; [13]China Medical University Hospital, Taichung City, Taiwan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Storr Liver Centre, Westmead Institute for Medical Research, University of Sydney, Sydney, NSW, Australia

Background

- The prevalence of chronic hepatitis C virus (HCV) infection in the Asia-Pacific region and Russia varies from 1-5%[1]
- Elbasvir (EBR) is a once-daily HCV NS5A inhibitor and grazoprevir (GZR) is a once-daily HCV NS3/4A protease inhibitor (**Figure 1**)
  - The fixed-dose combination (FDC) of EBR and GZR is approved in the European Union, United States, Canada, and several counties within the Asia-Pacific region for the treatment of HCV genotype (GT)1 and 4 infection[2]
    - Broad activity vs most HCV genotypes in vitro[3-5]
    - Efficacious in treatment-naive and -experienced participants, cirrhotic and noncirrhotic participants, HIV/HCV co-infected participants, and those with chronic kidney disease[6-9]
  - The C-CORAL trial was conducted in the Asia-Pacific region and Russia where data on the safety and efficacy of EBR/GZR are limited

Figure 1. EBR/GZR



Aim

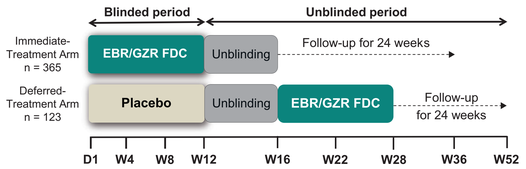
- To assess the efficacy and safety profile of EBR/GZR in people with HCV infection from mainland China, South Korea, Taiwan, Vietnam, Thailand, Australia, and Russia

Participants and Methods

Study Design

- C-CORAL (NCT02251990; Protocol PN-5172-067) was a phase 3, randomized, parallel-group, double-blind, placebo-controlled trial (**Figure 2**)

Figure 2. C-CORAL Study Design



D, day; W, week.

- The EBR 50 mg/GZR 100 mg FDC tablet is given once daily without regard for food
- Participants were randomized 3:1 to the immediate- or deferred-treatment group (ITG or DTG, respectively)
  - ITG: EBR/GZR for 12 weeks + follow-up for 24 weeks
  - DTG: placebo for 12 weeks + 4 weeks' follow-up, then 12 weeks of active EBR/GZR treatment + follow-up for 24 weeks
- Randomization was stratified by cirrhosis status (noncirrhotic vs cirrhotic) and study site (country)

Participants

- Treatment-naive participants with HCV GT 1, 4, or 6 infection were enrolled from mainland China, South Korea, Taiwan, Vietnam, Thailand, Australia, and Russia
  - Genotyping was performed using the Abbott HCV Real Time Genotype II assay (all participants outside China had confirmation via NS5B amplicon sequence analysis)
- Participants with compensated cirrhosis were allowed to enroll; cirrhosis was defined by:
  - Liver biopsy prior to day 1 showing cirrhosis (METAVIR F4)
  - FibroScan® >12.5kPa within 12 months of enrollment
  - FibroTest score >0.75 AND an aspartate aminotransferase (AST):platelet ratio index of >2
- Individuals with HIV co-infection, a presence or history of ascites, gastric, or variceal bleeding, hepatic encephalopathy, or other signs/symptoms of decompensated liver disease were excluded

Endpoints

- Efficacy analysis
  - The primary endpoint was sustained virologic response 12 weeks after completion of treatment in the ITG (SVR12, HCV RNA <15 IU/mL [COBAS® TaqMan® v2.0])
    - This presentation presents SVR12 results from the combined ITG and DTG populations
  - The full analysis set (FAS) included all participants who received ≥1 dose of study drug
  - Safety analyses
    - Assessed in all participants who received ≥1 dose of study drug (All Participants as Treated)
    - Comparison of ITG (active) and DTG (placebo) during the blinded period
  - Emergence of viral drug resistance was assessed in participants who met criteria for virologic failure with HCV RNA >1000 IU/mL
    - NS5A loci associated with resistance at amino acid positions:
      - GT1: 28, 30, 31, 93
      - GT4/6: 24, 28, 30, 31, 32, 38, 58, 92, 93
      - Non-GT1 reference strains: GT4; ED43 (4a), GT6, EUHK2 (6a)

Results

Demographics and Characteristics

- Most participants had HCV GT1b infection (n = 391, 80%) and were Asian (n = 351, 72%) (**Table 1**)

Table 1. Participant demographics

	ITG: EBR/GZR (n = 365)	DTG: placebo followed by EBR/GZR (n = 123)	Total (N = 488)
Age, years, mean (SD)	48.1 (13)	48.6 (13)	48.3 (13)
Male, n (%)	160 (44)	56 (46)	216 (44)
Race, n (%)			
Asian	263 (72)	88 (72)	351 (72)
White	101 (28)	35 (28)	136 (28)
Other	1 (<1)	0 (0)	1 (<1)
HCV genotype, n (%)			
1a	26 (7)	11 (9)	37 (8)
1b	293 (80)	98 (80)	391 (80)
4	2 (<1)	1 (<1)	3 (<1)
6	39 (11)	12 (10)	51 (11)
Baseline HCV RNA >800,000 IU/mL, n (%)	250 (69)	86 (70)	336 (69)
Cirrhosis, n (%)	67 (18)	23 (19)	90 (18)
Baseline ALT, IU/L, mean (SD)	64 (55)	70 (54)	66 (55)

ALT, alanine aminotransferase; SD, standard deviation.

Virologic Response

- In the FAS, SVR12 was achieved by 94.2% and 95.0% of participants in the ITG and DTG, respectively (**Figure 3**)
- In the ITG and DTG combined population, 27 participants failed to attain SVR12
  - 18 participants relapsed
  - 7 participants had on-treatment virologic failure (breakthrough/rebound)
  - 2 participants discontinued for administrative reasons

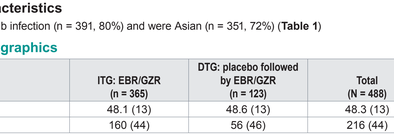
Figure 3. SVR12 in the FAS population

	ITG	DTG	All Participants
Non-SVR	21	6	27
Breakthrough/rebound	6	1	7
Relapse	14	4	18
Discontinued for administrative reasons	1	1	2

†Two participants did not receive active treatment in the DTG group after completing placebo treatment.

- SVR12 was high among participants with HCV GT1b or 4 infection (**Figure 4**)
- 92% of participants with HCV GT1a infection achieved SVR12
- SVR12 was lowest in participants with HCV GT6 infection
  - Of the 25 participants with virologic failure in this study, 17 had HCV GT6 infection

Figure 4. SVR12 by HCV genotype (FAS population)

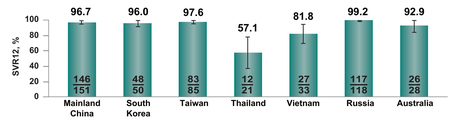


	GT1a	GT1b	GT1-other	GT4	GT6
Non-SVR	3	7	0	0	17
Breakthrough/rebound	0	0	0	0	7
Relapse	3‡	5	0	0	10
Discontinued for administrative reasons†	0	2	0	0	0

†Unrelated to study medication.
‡2 of the 3 participants with GT1a infection who relapsed had baseline NS5A RAS.

- Lower rates of SVR12 in Thailand and Vietnam were due to high rates of virologic failure among participants with HCV GT6 infection (**Figure 5**)

Figure 5. SVR12 by country of enrollment and genotype (FAS population)



	Mainland China	South Korea	Taiwan	Thailand	Vietnam	Russia	Australia
GT1a	—	1/1	5/5	4/6	12/12	3/3	9/10
GT1b	136/140	47/49	69/69	4/4	5/5	113/114	8/8
GT1-other	6/6	—	—	—	—	—	—
GT4	—	—	—	—	—	1/1	2/2
GT6	4/5	—	9/11	4/11	10/16	—	7/8

- SVR12 varied according to GT6 subtype (**Table 2**)
  - The 6 participants with HCV GT6f infection had a notably low response rate (17%); including 5 participants with on-treatment virologic failure

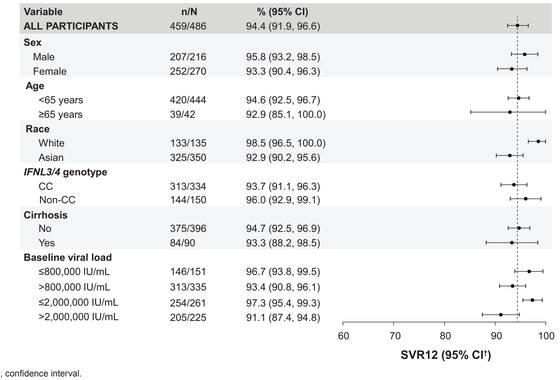
Table 2. SVR12 according to HCV GT6 subtype

GT6 subtype	Country	SVR12, % (n/N)	Type of failure
6-ns	China, n = 5 Taiwan, n = 1	83 (5/6)	1 relapse
6a	Taiwan, n = 1 Vietnam, n = 3	25 (1/4)	1 OTF, 2 relapse
6c	Thailand, n = 1	0 (0/1)	1-OTF
6e	Australia, n = 1 Vietnam, n = 7	75 (6/8)	2 relapse
6f	Thailand, n = 6	17 (1/6)	5 OTF
6g	Taiwan, n = 3	66 (2/3)	1 relapse
6h	Vietnam, n = 3	100 (3/3)	—
6i	Thailand, n = 1	100 (1/1)	—
6k	Vietnam, n = 1	100 (1/1)	—
6l	Vietnam, n = 1	100 (1/1)	—
6m	Australia, n = 6	83 (5/6)	1 relapse
6n	Taiwan, n = 2 Australia, n = 1 Thailand, n = 3	67 (4/6)	2 relapse
6q	Vietnam, n = 1	0 (0/1)	1 relapse
6w	Taiwan, n = 4	100 (4/4)	—
Total		**67 (34/51)**	**10 relapse/7 OTF**

OTF, on-treatment failure (either breakthrough or rebound).

- SVR12 by participant subgroup is shown in **Figure 6**

Figure 6. SVR12 by participant subgroup (FAS population)

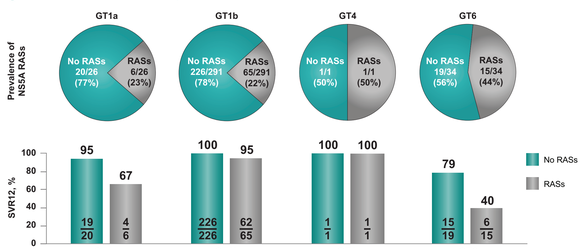


CI, confidence interval.
†Asymptotic CI for proportion.

Resistance Analyses

- Resistance-associated substitutions (RASs) had no impact on SVR rates in participants with GT1b or 4 infection (**Figure 7**)
  - Efficacy was reduced in the small number of GT1a- or 6-infected participants with baseline NS5A RASs

Figure 7. Prevalence and impact on SVR12 of NS5A RASs



The resistance analysis population includes participants with available sequence data (ITG only) and excludes those who discontinued from the study for reasons unrelated to treatment. Chinese participant sequence data are only available for those with HCV GT1b infection. The presence of RASs was assessed using population or next generation sequencing with approximate cutoff values of 25% and 15%, respectively.

Safety

- Administration of EBR/GZR was generally safe and well tolerated (**Table 3**)

Table 3. Safety and Tolerability

	ITG: EBR/GZR (n = 365)	DTG: placebo (n = 123)	DTG: EBR/GZR (n = 121)
Safety summary	n (%)	n (%)	n (%)
At least one AE	186 (51)	62 (50)	44 (36)
Drug-related AE	78 (21)	26 (21)	13 (11)
SAEs†	5 (1)	2 (2)	3 (3)
Serious drug-related AE	0 (0)	0 (0)	1‡ (1)
Discontinuations due to AE§	1 (<1)	1 (<1)	2 (2)
Deaths‖	1 (<1)	0 (0)	0 (0)
Late ALT/AST elevation¶			
>2.0-5.0× ULN	5 (1.4)	3 (2.5)	2 (1.7)
>5.0× ULN	4 (1.1)	0 (0)	3 (2.5)
Total bilirubin††			
>5.0× baseline	1 (0.3)	0 (0)	1 (0.8)

AE, adverse event; SAE, serious adverse event; ULN, upper limit of normal.
†SAEs were suicide, Evan's syndrome, contusion, enteritis, and gastric lymphoma in the ITG; influenza and metatarsal fracture in the placebo phase of the DTG; and paroxysmal atrial fibrillation, ankle fracture, and uterine hemorrhage in the EBR/GZR phase of the DTG. Only the paroxysmal atrial fibrillation was considered related to study medication by the investigator. All resolved with no action necessary except suicide (and gastric lymphoma which is ongoing).
‡DTG (EBR/GZR); 1 participant developed paroxysmal atrial fibrillation noted on electrocardiogram performed on the last day of treatment with EBR/GZR. Atrial fibrillation resolved within 24 hours after initiation of medical management.
§ITG: 1 participant met protocol-defined discontinuation criteria (elevation in ALT >3× ULN and bilirubin >2× ULN); DTG (placebo): 1 participant had constellation of nonserious but related AEs (hypoesthesia oral, chest discomfort, and headache) at day 7; DTG (EBR/GZR): 2 participants met the protocol-defined discontinuation criteria with ALT >500 IU/L.
‖One participant in the ITG withdrew and subsequently committed suicide (deemed unrelated to study drug).
¶ALT/AST elevations occurring after treatment week (TW)4 in participants with an occurrence of ALT/AST ≤ULN between TW2 and 4.
††Increase in bilirubin led to discontinuation from study drug in a participant in the ITG who ingested alcohol 2 days prior.

- Late ALT/AST elevations
  - 5 of 486 randomized participants (1%) experienced late alanine aminotransferase (ALT) elevations >5× ULN. None had evidence of hepatic synthetic dysfunction or concomitant total bilirubin >2× ULN. Two of these participants (0.4%) discontinued (one at TW6, the other at TW10) due to meeting the protocol–defined stopping criteria of ALT >500 IU/L and both achieved SVR12. The remaining 3 participants had reductions in ALT while continuing on EBR/GZR
  - Two participants experienced late AST elevations, and neither had concomitant ALT >100 IU/L. Both of these participants reported increased physical activity prior to lab work
- Bilirubin elevations
  - In the ITG, increased bilirubin levels led to treatment discontinuation of a participant who ingested alcohol 2 days prior to labs. This participants' total bilirubin increased from 0.42 at baseline to 4.06 at treatment week (TW)6. At this time, the participant met the prespecified criteria for discontinuation at TW6 with an ALT value >3× nadir ALT (from 30 U/L to 112 U/L) and a simultaneous total bilirubin level that was >2× ULN, and discontinued study medication. This patient achieved SVR12
  - In the DTG, one participant had an isolated elevation in total bilirubin at TW4 (from 0.44 to 2.70 mg/dL with a direct fraction of 0.97) and no other liver function test abnormalities. Total bilirubin was normalized by TW6

Conclusions

- Treatment with a 12-week regimen of EBR/GZR achieved an SVR12 of 94% in a heterogeneous population with HCV GT 1, 4 or 6 infection
  - High SVR12 rates in participants with GT1a (92%), GT1b (98%), or GT4 (100%) infection
  - Lower SVR12 in those with HCV GT6 infection, notably in a small number of participants with GT6a (25%) or 6f (17%)
- SVR12 was similar regardless of baseline sex, age, or cirrhosis status
- The efficacy of a 12-week regimen of EBR/GZR was not impacted by the presence of baseline NS5A or NS3 RASs in HCV GT1b- or 4-infected participants
  - Efficacy was reduced in the small number of HCV GT1a- or 6-infected participants with baseline NS5A RASs
- Administration of EBR/GZR was generally safe and well tolerated

References

1. Lim SG, Dan YY. *Korean J Intern Med.* 2015;30:423-433.
2. Zepatier [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2017.
3. Summa V et al. *Antimicrob Agents Chemother.* 2012;56:4161-4167.
4. Harper S et al. *ACS Med Chem Lett.* 2012;3:332-336.
5. Coburn CA et al. *ChemMedChem.* 2013;8:1930-1940.
6. Kwo P et al. *Gastroenterology.* 2017;152:164-175.e4.
7. Roth D et al. *Lancet.* 2015;386:1537-1545.
8. Rockstroh JK et al. *Lancet HIV.* 2015;2:e319-e327.
9. Zeuzem S et al. *Ann Intern Med.* 2015;163:1-13.

Acknowledgments

- We extend our gratitude to the participants, their families, investigators, and site personnel who participated in this study
- The principal investigators of C-CORAL were: **Australia**: Wendy Cheng, Jacob George; **China**: Zhongping Duan, Wenxiang Huang, Yan Huang, Jidong Jia, Zhansheng Jia, Wen Xie, Guijie Xin, Fusheng Wang, Maorong Wang, Lai Wei, Shanming Wu, Mingxiang Zhang, Yingren Zhao; **Russia**: Igor Gennadyevich Bakulin, Pavel Bogomolov, Eduard Z. Burnevich, Evgeny Chesnokov, Vasiliy Isakov, Svetlana Kizhlo, Marina Maevskaya, Igor Nikitin, Elena Nikulkina, Elena Nurmukhametova, Pavel P. Ogurtsov, Olga Olegovna, Vadim Valentinovich Pokrovsky, Olga Sagalova, Konstantin V. Zhdanov; **South Korea**: Woo Jin Chung, Jeong Heo, Do Young Kim, Yoon-Jun Kim, Youn-Jae Lee, Won-Young Tak; **Taiwan**: Pin-Nan Cheng, Chi-Jen Chu, Wan-Long Chuang, Tsung-Hui Hu, Cheng-Yuan Peng, I-Shyan Sheen, Sheng-Shun Yang; **Thailand**: Abhasnee Sobhonslidsuk, Tawesak Tanwandee, Satawat Thongsawat; **Vietnam**: Manh Hung Le, Van Kinh Nguyen, Thi Thu Thuy Pham
- Medical writing assistance was provided by Tim Ibbotson, PhD, of ApotheCom (Yardley, PA, USA) and funded by Merck & Co., Inc.