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Concomitant Proton Pump Inhibitor Use Does Not Reduce the Efficacy of Elbasvir/Grazoprevir

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Background

- Up to one third of hepatitis C virus (HCV)-infected patients use acid-reducing agents or proton pump inhibitors (PPIs)[1]
- It has been noted that sustained intragastric pH elevation can meaningfully decrease the bioavailability, and hence the concentration, of NS5A protein inhibitors (including the direct-acting antiviral agents ledipasvir and velpatasvir).[2,3] These reduced concentrations may decrease efficacy
- Grazoprevir (GZR), a potent once-daily NS3/4A protease inhibitor, and elbasvir (EBR), a potent once-daily NS5A protein inhibitor, are components of a fixed-dose combination (EBR/GZR FDC) therapy indicated for the treatment of chronic HCV genotype (GT) 1 or 4 infection[4-6]
  - EBR is prepared using an enabled formulation that reduces the negative pH effect on its bioavailability[7]
  - GZR is an acidic compound; therefore, an increase in gastric pH is not expected to reduce its bioavailability[7]
- In a Phase I study in healthy volunteers, administration of EBR/GZR FDC with or without PPIs resulted in comparable EBR and GZR pharmacokinetics (PK)[7]

Objectives

This *post hoc* analysis assessed the 12-week sustained viral response (SVR12) of the EBR/GZR FDC in subjects with self-reported PPI use utilizing pooled data from studies in the Phase 3 clinical program of EBR/GZR. In addition, the PK of EBR/GZR in a subset of these patients was also assessed.

Methods

- Data were derived from the 6 Phase 3 EBR/GZR trials that included treatment-naïve or treatment-experienced GT1- or GT4-infected subjects, with or without compensated cirrhosis
- The analysis incorporated data from only those Phase 3 trials in which the marketed FDC tablet of EBR/GZR (which included the enabled formulation of EBR) was used
- All studies were conducted in accordance with the principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. Patients provided written informed consent prior to any study procedures
- Subjects with HCV GT1 or 4 with baseline viral load >10,000 IU/mL, who were either treatment-naïve or prior treatment failures, and either cirrhotic or noncirrhotic, were included in these analyses
- In each study, subjects received EBR/GZR once daily, without regard to food intake, as either an FDC of EBR 50 mg/GZR 100 mg for 12 weeks or an FDC of EBR 50 mg/GZR 100 mg + RBV for 16 weeks. Use of PPIs and other acid-reducing agents was allowed

Statistics

- Analyses were done in the modified Full Analysis Set (mFAS) population, which excluded administrative discontinuations
- Self-reported consistent baseline PPI use was defined as ≥7 consecutive days of use between Day -7 and Day 7
- A series of bivariate logistic regression models was performed on the mFAS population to determine which factors were associated with achievement of SVR12 and to ascertain whether consistent PPI use had any effect
- Consistent PPI use was included in every bivariate model; other variables included in the analyses were gender, age (continuous and dichotomous [<64 years and ≥65 years]), cirrhosis status, prior treatment status, baseline HCV RNA (continuous and dichotomous [≤800,000 IU/mL and >800,000 IU/mL]), HCV genotype (1a, 1b, or 4), and presence of baseline resistance-associated variants (NS5A resistance-associated variants at amino acid positions 28, 30, 31, or 93)
- An additional set of multivariate logistic regression models was also considered using forward selection, backward selection, and stepwise selection procedures. All multivariate models included consistent PPI use, and a two-sided α=0.10 was used for inclusion and exclusion of the other variables from these models

Pharmacokinetics

- EBR population pharmacokinetic (PK) data were available for analysis from 5 of the 6 studies
- EBR area under the plasma concentration-time curve (AUC) and C_{max} for individual patients were estimated based on the EBR concentrations of sparsely collected pharmacokinetic samples using a population PK modeling approach
- The population PK model EBR was developed based on pooled PK data from subjects in Phase 1 to Phase 3 studies
- The model was evaluated using simulation-based visual predictive checks and showed that the model accurately characterized the central tendency of the observed data and that an appropriate distribution of the observed data fell within the 5th and 95th percentiles of model-simulated data. These results indicate that the models adequately describe the EBR concentration data from the clinical studies
- All statistical analyses were conducted using SAS 9.3

Results

Table 1. Baseline characteristics in the modified Full Analysis Set population

	Consistent Baseline PPI Use n=162	No Consistent Baseline PPI Use n=1,160	All Patients N=1,322
Gender, n (%)			
Male	104 (64.2)	758 (65.3)	862 (65.2)
Female	58 (35.8)	402 (34.7)	460 (34.8)
Age, mean (SD)	55.9 (8.4)	50.4 (10.9)	51.1 (10.8)
BMI, kg/m^2, mean (range)	27.7 (15.8, 47.8)	26.2 (11.0, 52.8)	26.3 (11.0, 52.8)
Race, n (%)			
White	108 (66.7)	850 (73.3)	958 (72.5)
Black	44 (27.2)	191 (16.5)	235 (17.8)
Asian	4 (2.5)	94 (8.1)	98 (7.4)
Other	6 (3.7)	25 (2.2)	31 (2.3)
Cirrhosis Status, n (%)			
Yes	47 (29.0)	237 (20.4)	284 (21.5)
No	115 (71.0)	923 (79.6)	1038 (78.5)
Prior Treatment Status, n (%)			
Treatment Experienced	43 (26.5)	212 (18.3)	255 (19.3)
Treatment Naïve	119 (73.5)	948 (81.7)	1067 (80.7)
Baseline HCV RNA			
≤800,000 IU/mL	39 (24.1)	379 (32.7)	418 (31.6)
>800,000 IU/mL	123 (75.9)	781 (67.3)	904 (68.4)
HCV Genotype, n (%)			
1a	105 (64.8)	643 (55.4)	748 (56.6)
1b	50 (30.9)	431 (37.2)	481 (36.4)
4	7 (4.3)	86 (7.4)	93 (7.0)
Presence of Baseline RAVs	17 (10.5)	158 (13.7)†	175 (13.3)†

†Presence of any variant in NS5A amino acid positions 28, 30, 31, or 93 at baseline. 5 subjects did not have baseline NS5A sequencing performed and are thus excluded from the denominators for No consistent BL PPI Use and All Patients for this term.

Table 2. SVR12 rates by key baseline demographic factors

Consistent PPI usage was not a statistically significant effect, regardless of adjustment for the factors considered

Model Category	Demographic/ Baseline Parameter	Consistent Baseline PPI Use Observed SVR12 Rate (n/N) (95% CI)	No Consistent Baseline PPI Use Observed SVR12 Rate (n/N) (95% CI)
Overall	–	95.7% (155/162) (91.3, 98.2)	97.3% (1129/1160) (96.2, 98.2)
Gender	Female	96.6% (56/58) (88.1, 99.6)	98.5% (396/402) (96.8, 99.5)
	Male	95.2% (99/104) (89.1, 98.4)	96.7% (733/758) (95.2, 97.9)
Age	<64 years	95.7% (133/139) (90.8, 98.4)	97.4%(1047/1075) (96.3, 98.3)
	≥65 years	95.7% (22/23) (78.1, 99.9)	96.5% (82/85) (90.0, 99.3)
Cirrhosis Status	Cirrhotic	93.6% (44/47) (82.5, 98.7)	97.9% (232/237) (95.1, 99.3)
	Non-Cirrhotic	96.5% (111/115) (91.3, 99.0)	97.2% (897/923) (95.9, 98.2)
Prior Treatment Status	Treatment Experienced	95.3% (41/43) (84.2, 99.4)	98.1% (208/212) (95.2, 99.5)
	Treatment Naïve	95.8% (114/119) (90.5, 98.6)	97.2% (921/948) (95.9, 98.1)
Baseline HCV RNA Category (≤800,000 vs >800,000)	≤800,000	100% (39/39) (91.0, 100.0)	98.7% (374/379) (96.9, 99.6)
	>800,000	94.3% (116/123) (88.6, 97.7)	96.7% (755/781) (95.2, 97.8)
HCV Genotype	GT 1a	94.3% (99/105) (88.0, 97.9)	96.0% (617/643) (94.1, 97.3)
	GT 1b	100% (50/50) (92.9, 100.0)	99.1% (427/431) (97.6, 99.7)
	GT 4	85.7% (6/7) (42.1, 99.6)	98.8% (85/86) (93.7, 100.0)
Presence of Baseline RAVs†	BL RAVs Present	82.4% (14/17) (56.6, 96.2)	88.6% (140/158) (82.6, 93.1)
	No BL RAVs Present	97.2% (141/145) (93.1, 99.2)	98.7% (984/997) (97.8, 99.3)

†Presence of any variant in NS5A amino acid positions 28, 30, 31, or 93 at baseline. Note, 5 subjects did not have baseline NS5A sequencing performed and are thus excluded from this summary. All 5 subjects were classified as having no consistent baseline PPI use.

Figure 1A. Distribution of EBR AUC by SVR12 status and PPI use with at least 7 consecutive days of PPI use within Days -7 to 7

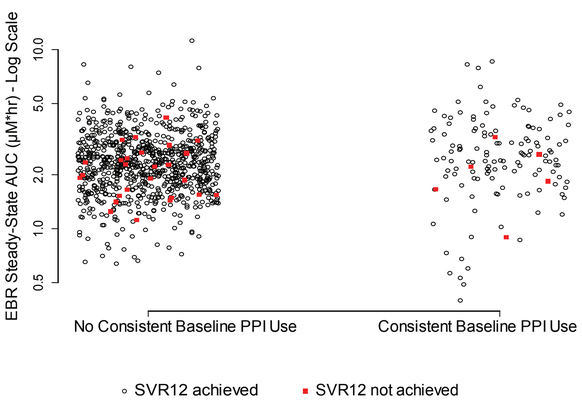

Figure 1B. Distribution of EBR C_{max} by SVR12 status and PPI use with at least 7 consecutive days of PPI use within Days -7 to 7

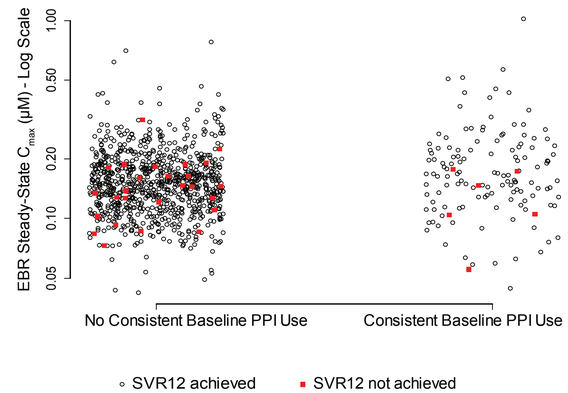

Table 3. Geometric mean AUC_{0-24} and C_{max} in subjects taking EBR with and without consistent baseline PPI use

PK Parameter (EBR)	No Consistent Baseline PPI Use N	No Consistent Baseline PPI Use Value (95% CI)	Consistent Baseline PPI Use N	Consistent Baseline PPI Use Value (95% CI)
GM AUC_{0-24} (μM•hr)	869	2.28 (2.22, 2.35)	136	2.42 (2.26, 2.59)
GM C_{max} (μM)	869	0.15 (0.15, 0.15)	136	0.17 (0.16, 0.18)

Summary

- The results of this *post hoc* analysis showed that PPIs taken concomitantly for at least 7 consecutive days were not associated with reduced SVR12 rates with EBR/GZR treatment
- When included in logistic regression analyses, consistent PPI use was not a predictive factor in SVR12 achievement, even after adjusting for effects known to be associated with SVR12 or for which there was an imbalance between consistent PPI users and inconsistent PPI users
- The population PK results further support these findings, demonstrating no correlation between consistent PPI use, EBR AUC_{0-24}, and SVR12 rate

Conclusions

- In conclusion, there is no clinically significant effect of consistent concomitant PPI use with EBR/GZR on SVR12 rates in HCV patients with and without cirrhosis infected with GT1 or GT4
- Furthermore, consistent PPI use was not associated with changes in SVR12 rates in subjects based on age, cirrhotic state, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants

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Potential Competing Interests

Nancy Reau: Research support: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Merck; Consultant: AbbVie, Bristol-Myers Squibb, Gilead, Merck.

Michael N. Robertson, Hwa-Ping Feng, Luzelena Caro, Wendy W. Yeh, Bach-Yen T. Nguyen, Janice Wahl, Eliav Barr, Peggy Hwang, and Stephanie O. Klopfer: Employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock or hold stock options in the company.