Efficacy and Safety of Bemnifosbuvir and Ruzasvir After 8 Weeks of Treatment in Patients With Chronic Hepatitis C Virus (HCV) Infection

TOP-251

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INTRODUCTION

- Hepatitis C virus (HCV) infection is increasingly impacting younger individuals, with injection drug use being the most common risk factor. Although rates of cirrhosis are low (estimated ~15%), associated comorbidities, social factors, and co-medications can complicate treatment of HCV[1–3]
- Novel direct-acting antiviral (DAA) regimens that are convenient, short duration, with low risk of drug–drug interactions, and with no food effect, have the potential to improve upon the limitations of current therapies for today's population
- Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic inhibitors of the HCV NS5B polymerase and the NS5A protein, respectively[4,5]
- This Phase 2, open-label, single-arm study is the first to evaluate the safety and efficacy of a novel BEM+RZR combination in patients with chronic HCV infection (NCT05904470)
- Data from a lead-in cohort (N=60), reporting a 97% rate of sustained virologic response at 12 weeks post treatment (SVR12), were presented previously.[6] Here, we present data from the full study cohort of 275 patients

METHODS

Study design

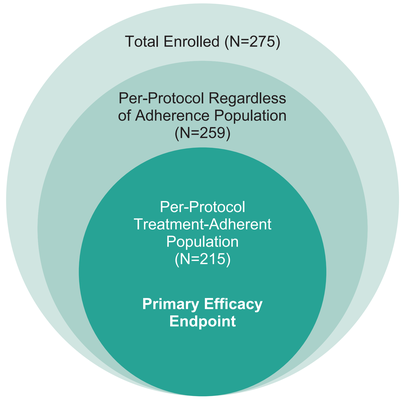
- Treatment-naïve adult patients with chronic HCV (either non-cirrhotic [NC] or with compensated cirrhosis [CC]) received 550 mg BEM (once daily) and 180 mg RZR (once daily) for 8 weeks
- Safety and tolerability were assessed in all patients who received at least one dose of study drug. Treatment-emergent adverse events (TEAEs) were those with onset date within the treatment period, defined as the time from first study drug administration to 4 weeks post treatment
- The primary efficacy endpoint was the proportion of patients achieving SVR12 in the Per-Protocol Treatment-Adherent Population: patients who were study-drug adherent, corroborated by plasma drug levels and pill count
- Secondary and other endpoints included SVR12 in the Per-Protocol Regardless of Adherence Population (those with outcomes regardless of study-drug adherence), virologic failure, SVR24, and on-treatment viral kinetics
- Plasma HCV RNA was evaluated using Roche cobas® 6800 systems, with a lower limit of quantitation (LLOQ) of 15 IU/mL
- Next-generation sequencing was performed at baseline and at the time of virologic failure (final analyses pending). Prevalence of resistance-associated substitutions (RASs) at baseline are described herein at the following amino acid positions (1% detection limit)
  - NS5A: 24, 25, 26, 28, 29, 30, 31, 32, 37, 38, 52, 54, 58, 62, 64, 91, 92, 93
  - NS5B: 15, 96, 142, 150, 159, 162, 179, 206, 223, 237, 282, 289, 293, 316, 320, 321

RESULTS

Baseline characteristics

- The majority of patients were infected with Genotype 1 (GT1; ~69%) or GT3 (28%)
- Cirrhosis was present in 13.5% of patients
- 18% of patients had a history of psychiatric disorders and 9% had a history of drug abuse
- RASs in NS5A and NS5B were present in 88% and 62% of patients, respectively, at baseline

Figure 1. Study population and analysis sets



Patient disposition

- 275 patients were enrolled and received the study drug, with 259 included in the Per-Protocol Regardless of Adherence Population
- 44 of the 259 patients (17%) were treatment non-adherent, leaving 215 patients in the Per-Protocol Treatment-Adherent Population (primary efficacy population) (**Figure 1**). Characteristics were consistent with the total study population (**Table 1**)

Table 1. Baseline demographic and disease characteristics

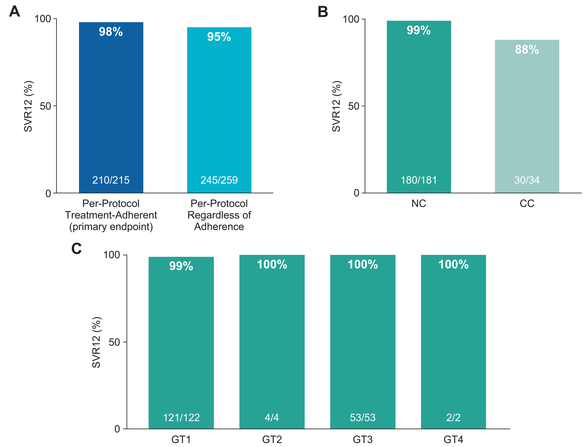
Characteristic	Per-Protocol Treatment-Adherent (N=215)	Total Enrolled (N=275)
Mean age, years (range)	50.5 (20–85)	49.6 (20–85)
Mean BMI, kg/m² (SD)	26.5 (4.7)	26.4 (4.9)
Male sex, n (%)	100 (46.5)	144 (52.4)
Race, n (%)		
Asian	44 (20.5)	55 (20.0)
Black/African American	6 (2.8)	11 (4.0)
White	156 (72.6)	192 (69.8)
Other	9 (4.2)	17 (6.2)
HCV genotype, n (%)		
GT1	151 (70.2)	189 (68.7)
GT2	4 (1.9)	7 (2.5)
GT3	58 (27.0)	77 (28.0)
GT4	2 (0.9)	2 (0.7)
Cirrhosis status, n (%)		
NC	181 (84.2)	238 (86.5)
CC	34 (15.8)	37 (13.5)

BMI, body mass index; SD, standard deviation.

Efficacy analysis

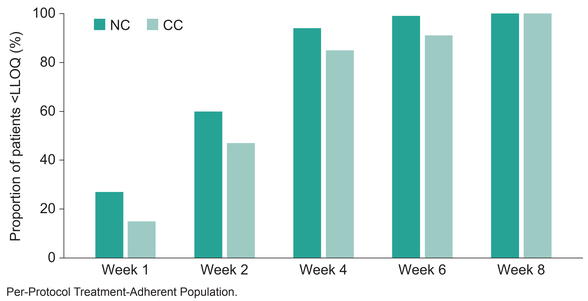
- Overall, SVR12 was 98% in the Per-Protocol Treatment-Adherent Population (primary endpoint) and 95% in the Per-Protocol Regardless of Adherence Population (**Figure 2A**)
- In the Per-Protocol Treatment-Adherent Population, SVR12 was higher for patients with NC (99%) vs patients with compensated cirrhosis CC (88%) (**Figure 2B**)
- In NC patients, high SVR12 was observed across genotypes, including GT3 (**Figure 2C**)
- Although viral kinetics were slower in CC patients vs NC, all patients with CC achieved HCV RNA <LLOQ by Week 8 (**Figure 3**)
- Long-term durability of response was sustained as there were no virologic failures between 12 and 24 weeks post treatment

Figure 2. SVR12



SVR12 rates are presented by analysis set (A), according to cirrhosis (NC vs CC) in the Per-Protocol Treatment-Adherent Population (B), and according to GT among NC patients in the Per-Protocol Treatment-Adherent Population (C).

Figure 3. On-treatment viral response



Per-Protocol Treatment-Adherent Population.

Analysis of virologic failure (VF)

- In the Per-Protocol Treatment-Adherent Population, VF occurred in one NC patient (0.6% of NC) and four CC patients (12% of CC)
  - The NC patient was infected with GT1a, and the four CC patients had GT1a (n=2), 1b (n=1), and 3a (n=1)
  - All VFs were relapses that occurred at 4 weeks post treatment
- Analysis of viral kinetics and plasma drug exposures across the whole study population (N=275) indicated that the majority of VFs were due to treatment adherence issues

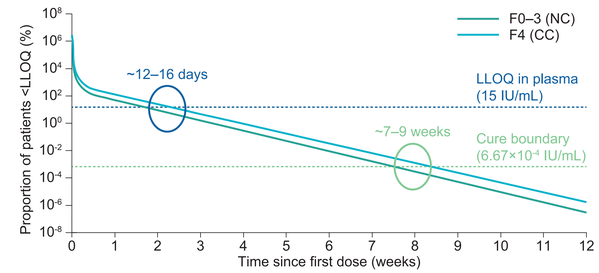
Safety and tolerability

- BEM+RZR was generally well tolerated
- TEAEs were reported in 43% (118/275) of patients. Most TEAEs were mild to moderate in intensity, with headache (9%) and nausea (8%) being the most commonly reported
- Treatment-emergent serious AEs (SAEs) were reported in 3% (9/275) of patients, with 1 resulting in death (carcinoma). An additional 10 subjects (4%) reported SAEs that occurred at least 4 weeks after discontinuation of study drug, four of which resulted in death. None of the SAEs were assessed as related to study drug
- There were no study-drug-related premature treatment discontinuations, and no clinically relevant trends in laboratory or ECG abnormalities

Viral kinetic modeling

- Data from the study were evaluated in a multiscale model of HCV infection to predict the on-treatment viral response with the BEM/RZR regimen (**Figure 4**)
- Predicted time to HCV RNA <LLOQ was ~12 days and ~16 days for F0–F3 (NC) and F4 (CC) patients, respectively
- Predicted time to cure was ~7.5 weeks and ~8.4 weeks for F0–F3 (NC) and F4 (CC) patients, respectively

Figure 4. Model-predicted viral kinetics*



Per-Protocol Treatment-Adherent Population. CC, compensated cirrhotic; F, fibrosis stage; NC, non-cirrhotic.

CONCLUSIONS

- In this Phase 2 study of BEM+RZR in HCV-infected patients, a high SVR12 rate (98%) was observed in treatment-adherent patients with a short 8-week treatment
  - A high SVR12 rate (95%) was also observed regardless of treatment adherence (16.8% of patients were non-adherent)
  - Compared with non-cirrhotic patients, who had 99% SVR12 (regardless of genotype), those with compensated cirrhosis had lower SVR12 (88%)
- While viral kinetics were slower in those with compensated cirrhosis, patients achieved HCV RNA <LLOQ by end of treatment at Week 8, suggesting that a 12-week duration of treatment in this population will maximize efficacy
  - Exploratory viral kinetic modeling further supports time-to-cure estimates of 12 weeks for those with compensated cirrhosis
- Rates of virologic failure were low, and there were no clear patterns relating to impact of baseline RASs on SVR12 rates
- BEM+RZR was well tolerated, with no study-drug-related SAEs or treatment discontinuations
- Data support the ongoing clinical development of BEM+RZR as a potential best-in-class HCV DAA with low risk of DDIs and no food effect; the regimen is currently being evaluated in Phase 3 studies (NCT06868264)

References

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Acknowledgments

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Disclosures

SL, MM, SI, QH, XJZ, KP, BB, AH, and JH are employees of and may own stock in Atea Pharmaceuticals.

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