Lead-in Cohort Results From a Phase 2 Study of a Novel 8-week Combination Regimen of Bemnifosbuvir and Ruzasvir in Patients With Chronic Hepatitis C Virus Infection

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INTRODUCTION

- Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic inhibitors of the HCV NS5B polymerase and the NS5A protein, respectively.[1–4] The combination of BEM+RZR has demonstrated potent *in vitro* synergistic antiviral activity[5]
- This ongoing Phase 2, open-label, single-arm study is the first to evaluate BEM+RZR in subjects with chronic HCV infection.[6] Results from the lead-in cohort are presented (N=60)

METHODS

- Treatment-naïve subjects with chronic HCV received the combination of 550 mg BEM once daily (QD) and 180 mg RZR QD for 8 weeks. The Phase 2 formulation comprised two tablets of BEM and two capsules of RZR
- Plasma HCV RNA was evaluated using the Roche cobas® HCV quantitative nucleic acid test for use on the cobas® 6800/8800 systems, with a lower limit of quantitation (LLOQ) of 15 IU/mL
- An SVR4 rate of ≥90% in a lead-in cohort of subjects without cirrhosis was required to proceed with further enrollment and complete the study

RESULTS

Subject disposition and baseline characteristics

- 60 subjects in the lead-in cohort were enrolled and completed the 8-week treatment period (**Table 1**)
- The majority of subjects were infected with genotype 1b (GT1b) (65%) and GT3 (21.7%). Subjects included in the lead-in did not have cirrhosis; 10 of 60 (16.7%) had F3 fibrosis

Table 1. Baseline demographic and disease characteristics

Characteristic	Subjects (N=60)
Median age, years (range)	47 (25–79)
Median BMI, kg/m² (range)	26.3 (18.9–47.1)
Male sex, n (%)	34 (56.7)
Race, n (%)	
White	57 (95.0)
Black or African American	1 (1.7)
Other	2 (3.3)
HCV genotype, n (%)	
GT1a	6 (10.0)
GT1b	39 (65.0)
GT2b	2 (3.3)
GT3	13 (21.7)
Median baseline viral load, log_{10} (range)	6.3 (4.2–7.3)
Fibrosis stage, n (%)	
F0	9 (15.0)
F1	26 (43.3)
F2	15 (25.0)
F3	10 (16.7)

Efficacy analysis

- All subjects completed treatment, with 54/60 (90%) achieving HCV RNA <LLOQ by Week 4 and all 60 achieving <LLOQ levels at the end of treatment (**Figure 1**). These rapid viral kinetics were observed in all subjects upon initiation of treatment, regardless of genotype and baseline viral load
- One subject withdrew consent after the Week 8 time point. SVR4 data were available in all 59 remaining subjects, with one documented post-treatment relapse, for an SVR4 rate of 58/59 (98%). Of the 58 subjects with SVR4, there was one non-HCV non-drug-related death before the SVR12 time point, with one additional post-treatment relapse documented, resulting in an SVR12 rate of 56/58 (97%) (**Figure 2**)
- High SVR12 rates were observed in both GT1 and historically difficult-to-treat GT3-infected subjects (**Figure 3**)

Figure 1. On-treatment viral kinetics: individual subject data

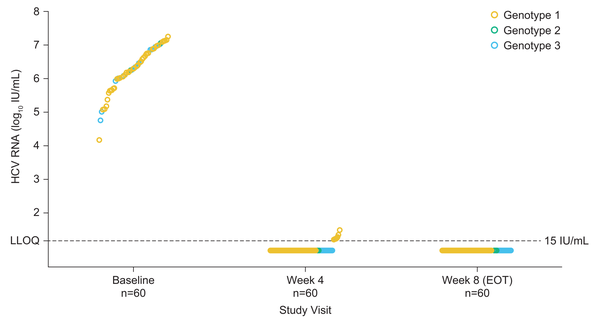
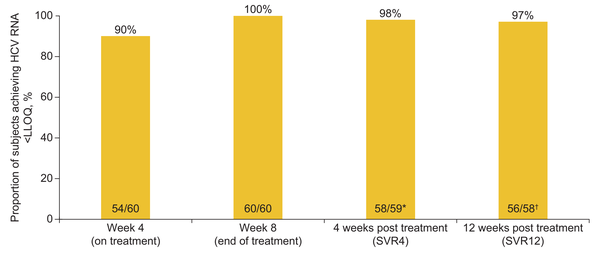
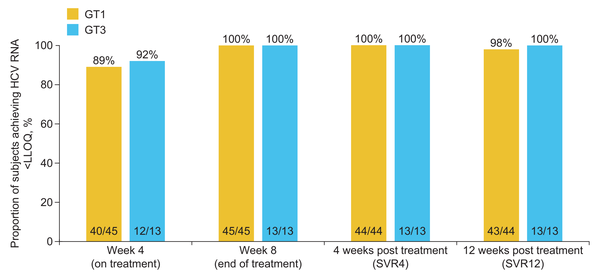


Figure 2. Proportion of subjects achieving <LLOQ by study visit



Two subjects with missing post-treatment data (one withdrew consent after Week 8*, and 1 non-drug-related death after SVR4†)

Figure 3. GT1- and GT3-infected subjects achieving <LLOQ



Safety and tolerability

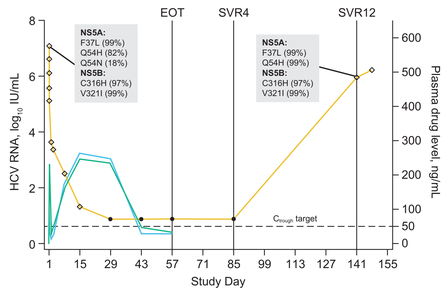
- The combination of BEM+RZR was well tolerated, with no adverse events (AEs) leading to treatment discontinuation
- One subject in the lead-in cohort experienced non-drug related serious AEs (SAEs) of cellulitis and subsequent overdose (not study drug), resulting in death after the SVR4 visit
- Other non-serious AEs were reported in 25% of subjects (15 of 60). Only headache was reported in more than a single subject (11.7%; 7 of 60 subjects). Non-serious AEs were mild or moderate in severity. No clinically significant patterns were observed for safety laboratory or electrocardiogram parameters

Analysis of post-treatment relapse

- Two subjects (GT1b and GT2b) experienced post-treatment relapse. Viral kinetics, plasma drug levels for AT-273 (surrogate for the BEM active triphosphate) and RZR, and resistance sequencing data from each are presented in **Figure 4**
- Both low plasma drug levels, and viral populations that were similar at baseline and SVR12 timepoints, indicate that relapse was due to treatment non-adherence, rather than viral resistance
- Post-study, both subjects were planned to be treated with SOF/VEL/VOX

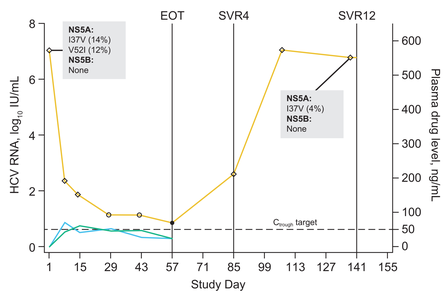
Figure 4. Profiles of subjects with relapse

A. GT1b-infected subject



Day	Plasma drug level, ng/mL	
	AT-273	RZR
1	BLQ	BLQ
8	161	173
15	246	263
29	235	248
43	45.7	**28.1**
57	**33.2**	**28.3**

B. GT2b-infected subject



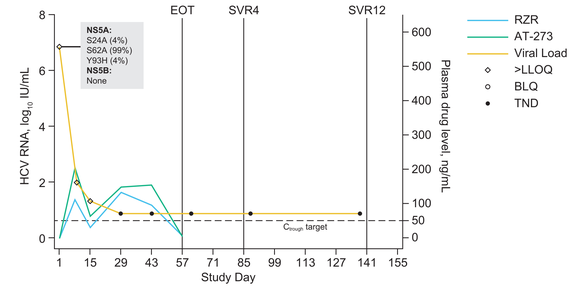
Day	Plasma drug level, ng/mL	
	AT-273	RZR
1	BLQ	BLQ
8	42.6	70.9
15	61.3	42.2
29	46.6	53.3
43	47.4	**27.6**
57	**24.4**	**24.4**

Kinetics of viral load, drug exposure and presence of NS5A/NS5B RASs are presented (left), alongside plasma drug levels at each timepoint (right). The horizontal dashed line represents the expected trough concentrations (C_{trough}) of BEM and RZR. LLOQ, lower limit of quantitation; BLQ, below limit of quantitation; EOT, end of treatment; TND, target not detected.

Additional sequencing analyses

- At baseline, most subjects (51/56) in the lead-in had at least one of the most common NS5A RASs, and 13/59 had at least one of the most common NS5B RASs (such as N142S, L159F, and V321I) with a 1% assay threshold cut-off:
  - NS5A aa: 24, 26, 28, 29, 30, 31, 32, 37, 38, 52, 54, 58, 62, 64, 92, or 93
  - NS5B aa: 96[a], 142[a], 159[a], 237[a,b], 282[a], 289[a], 320[a], 321[a,b] and 15[b], 223[b], 344[b] ([a]SOF RAS; [b]BEM *in vitro* RAS)
- A GT3-infected subject with pre-existing NS5A RASs S62A and Y93H achieved SVR12 (**Figure 5**)
  - S62A/Y93H (S62A+Y93H) confer very high resistance to NS5A inhibitors in GT3 replicons (>1000-fold loss of potency for RZR and velpatasvir; >100-fold loss of potency for pibrentasvir)
- Despite pre-existing baseline RASs at both targets, 97% of subjects achieved SVR12

Figure 5. GT3-infected subject with known NS5A RASs



CONCLUSIONS

- In this first clinical trial of BEM+RZR in HCV-infected subjects, a high SVR12 rate (97%) was observed in the lead-in cohort with a short 8-week duration of treatment
  - BEM+RZR has an excellent clinical resistance profile and has been shown to overcome baseline pre-existing RASs
  - Two post-treatment relapses were linked to treatment non-adherence as opposed to viral resistance
- Viral kinetics were similar in GT1- and GT3-infected subjects
  - 100% SVR12 rate in historically difficult-to-treat GT3-infected subjects
- The regimen was well tolerated, with no drug-related SAEs or treatment discontinuations
- Based on these data from the lead-in cohort, the Phase 2 study continues with the aim of enrolling up to an additional 220 subjects, including those with compensated cirrhosis

References

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6. https://clinicaltrials.gov/study/NCT05904470 (accessed May 2024)

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Disclosures

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

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