Up to 2 years' functional cure in response to bepirovirsen therapy in B-Clear Not-on-NA responders: B-Sure third report

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Bepirovirsen is an experimental medicine for the treatment of chronic hepatitis B. In this study, we measure durability of response to treatment. Some participants achieved functional cure after stopping bepirovirsen and maintained it for up to 2 years, to the point of the last follow up (maximum follow up of up to 2.5 years)

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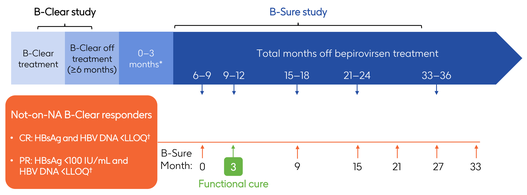
Background

- Functional cure, defined as sustained HBsAg loss and HBV DNA <LLOQ for 24 weeks off all treatment,[1] is regarded as the optimal treatment endpoint for chronic HBV infection, but is rarely achieved with current standard-of-care NA therapies[2–4]
- Bepirovirsen is an unconjugated antisense oligonucleotide that targets all HBV RNAs, including HBV messenger RNA and pregenomic RNA (reducing HBsAg and HBV DNA) and is currently being evaluated in the B-Well Phase 3 trials for the treatment of chronic HBV infection (NCT05630807, NCT05630820)[5–7]
- In the Phase 2b B-Clear study (NCT04449029), a subset of participants had a sustained response for 24 weeks after the end of bepirovirsen treatment; this occurred in participants On-NA and Not-on-NA[5]
- The ongoing Phase 2b B-Sure long-term durability study (NCT04954859) was initiated to generate long-term data on the durability of response in participants with a complete response (CR) or partial response (PR) off bepirovirsen treatment[8]
- Here, we present up to 2.5-year follow-up data on the durability of response for B-Clear Not-on-NA CR and PR participants who entered B-Sure
- Data for B-Clear On-NA participants are reported in poster THU-259

Methods

- The B-Sure study recruited B-Clear study responders (CR or PR at the end of the B-Clear study) for long-term follow-up
  - CR was defined as HBsAg and HBV DNA <LLOQ
  - PR was defined as HBsAg <100 IU/mL and HBV DNA <LLOQ
- Following entry into B-Sure, Not-on-NA participants were followed up at Months 3, 9, 15, 21, 27 and 33 (**Figure 1**). This is the third data review, with a cut-off date of 9 September 2024
- Participants maintaining a CR at Month 3 (i.e. at least 9 months off bepirovirsen, allowing for a 3-month washout period[9]) were considered to have achieved functional cure
- Adverse events were recorded at each visit to assess safety

Figure 1: **Study design**



*Time between B-Clear end-of-study and entry into B-Sure; †LLOQ is 0.05 IU/mL for HBsAg and 20 IU/mL for HBV DNA

Results

- From the B-Clear Not-on-NA participants, 11 CRs and 5 PRs enrolled into B-Sure (**Table 1**). As of the data cut-off date, these participants were continuing the trial

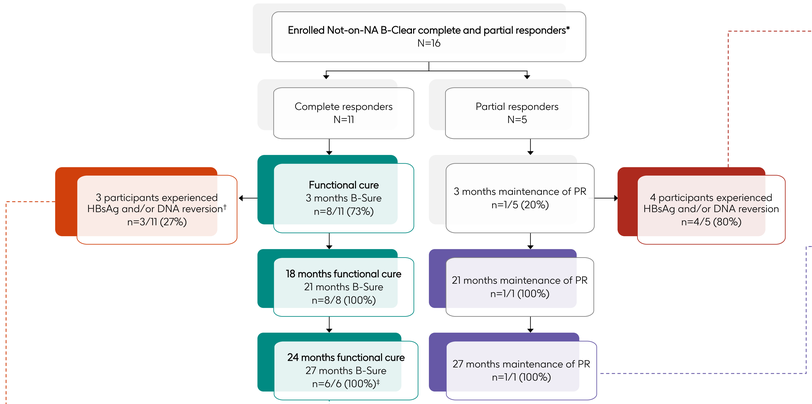
Table 1: **Baseline demographics and characteristics of participants in B-Sure who were Not-on-NA in B-Clear**

Characteristic	All participants N=17*
Age, mean (SD) years	44.1 (10.4)
B-Clear study treatment arm, n (%)	
Arm 1 (BPV 300 mg x 24W w/ LD)	9 (53)
Arm 2 (BPV 300 mg x 12W w/ LD then BPV 150 mg x 12W)	6 (35)
Arm 3 (BPV 300 mg x 12W w/ LD then Placebo x 12W)	2 (12)
Arm 4 (Placebo x 12W w/o LD then BPV 300 mg x 12W)	0 (0)
Probable duration of chronic HBV infection at B-Clear study baseline, n (%)	
<5 years	5 (29)
≥5–<10 years	2 (12)
≥10–<20 years	5 (29)
≥20 years	5 (29)
HBeAg status at B-Clear study baseline, n (%)	
Negative	17 (100)
Positive	0
HBsAg category at B-Clear study baseline, n (%)	
≤1000 IU/mL	9 (53)
>1000–≤3000 IU/mL	4 (24)
>3000 IU/mL	4 (24)
HBV DNA category at B-Clear study baseline, n (%)	
≤4 log_{10} IU/mL	7 (41)
>4–≤6 log_{10} IU/mL	9 (53)
>6 log_{10} IU/mL	1 (6)

*One non-responder from B-Clear was enrolled into B-Sure; this participant did not meet eligibility criteria but was enrolled in error

- Of the 11 CR participants, 8 (73%) maintained a CR at Month 3, thus achieving functional cure (**Figure 2**). All 8 participants maintained functional cure at 21 months of B-Sure
  - All 6 participants with Month 27 data (i.e. 33–36 months off-bepirovirsen) had maintained functional cure at this timepoint
- For PR participants, 1/5 maintained a PR at 3 months; this response was maintained to Month 27 of B-Sure (**Figure 2**)
  - Two PR participants started NA treatment after B-Sure enrolment
- After stopping bepirovirsen, there were no safety signals that suggested a latent adverse drug effect following treatment with bepirovirsen

Figure 2: **Flow diagram for Not-on-NA participants in B-Sure**



*One non-responder from B-Clear was enrolled into B-Sure in error and was excluded from the flow diagram; †One participant subsequently had seroclearance by Month 15 (Figure 3); ‡Only 6 of the 8 CRs had reached the 27-month follow-up timepoint at the data cut

Figure 3: **CR participant profiles**

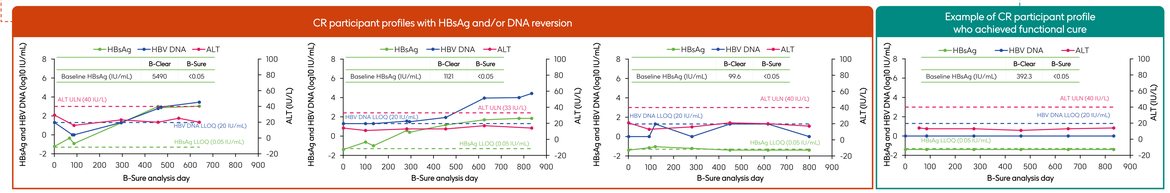
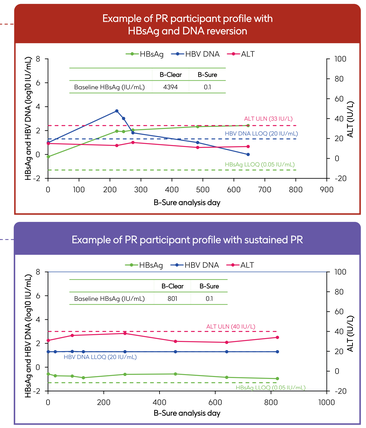


Figure 4: **PR participant profiles**



Conclusions

This global, long-term follow-up study provides further evidence for the durability of functional cure observed up to 2 years in response to bepirovirsen therapy, with no new safety signals observed

Clinical benefits (i.e. reduced HBsAg and HBV DNA) were particularly evident in participants who achieved a CR in the parent study; the potential benefits for participants with a PR are being further analysed

These findings provide evidence of the durability of functional cure observed with bepirovirsen

Abbreviations

ALT, alanine aminotransferase; BPV, bepirovirsen; CR, complete response; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LD, loading dose; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; PR, partial response; SD, standard deviation; W, weeks; w/, with; w/o, without; ULN, upper limit of normal

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