Up to 18 months' functional cure in response to bepirovirsen therapy in B-Clear On-NA responders: B-Sure third report

Lay summary: 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 all treatment and maintained it for up to 18 months, to the point of the last follow up (maximum follow up of up to 2.5 years).

Digital poster — SCAN ME

Narrated summary — SCAN ME

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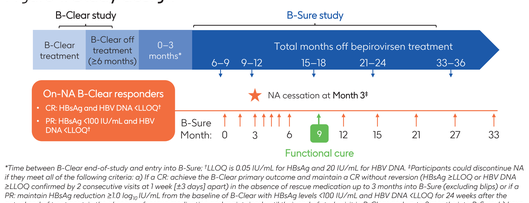
Background

- 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 On-NA CRs and PRs who entered B-Sure
- Data for B-Clear Not-on-NA participants are reported in poster TOP-268

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
- On-NA participants, if eligible, discontinued NAs 3 months after entry into B-Sure and were followed every 2 weeks in the first month after NA cessation, then every month in the next 3 months, and every 3 months up to Month 15. Subsequently, they were monitored every 6 months up to Month 33 (**Figure 1**). This is the third data review, with a cut-off of 9 September 2024
- Participants maintaining a CR at Month 9 (i.e. 6 months post NA cessation and 15–18 months off bepirovirsen) 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. ‡Participants could discontinue NA if they meet all of the following criteria: a) If a CR: achieve the B-Clear primary outcome and maintain a CR without reversion (HBsAg ≥LLOQ or HBV DNA ≥LLOQ confirmed by 2 consecutive visits at 1 week [±3 days] apart) in the absence of rescue medication up to 3 months into B-Sure (excluding blips) or if a PR: maintain HBsAg reduction ≥1.0 $\log_{10}$ IU/mL from the baseline of B-Clear with HBsAg levels <100 IU/mL and HBV DNA <LLOQ for 24 weeks after the actual end of treatment, in the absence of rescue medication and maintained until their end of study visit in B-Clear and up to 3 months into B-Sure; b) have stable NA treatment for 3 months into B-Sure; c) have ALT <1.25xULN at 2.5 months into B-Sure. Participants could resume NA treatment if they meet any of the following criteria: a) HBV DNA >20000 IU/mL; b) HBV DNA >2000 IU/mL after 2 sequential lab results confirmed within 1 week (±3 days) from the date of first result (with or without ALT elevation); c) Investigator has concern for the participant's safety and has discussed with the medical monitor.

Results

- From the B-Clear On-NA participants, 14 CRs and 26 PRs enrolled into B-Sure (**Table 1**). As of the data cut-off date, 38/40 (95%) participants were continuing the trial

Table 1: **Baseline demographics and clinical characteristics of participants in B-Sure who were On-NA in B-Clear**

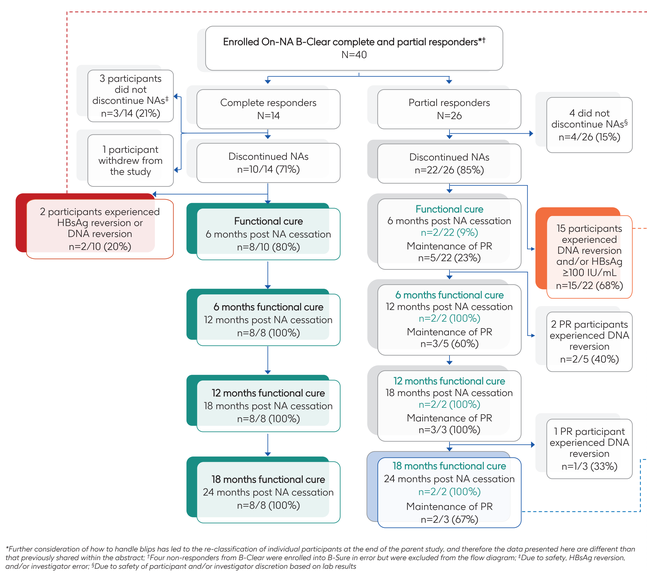
Characteristic	All participants N=44*
Age, mean (SD) years	53.8 (11.4)
B-Clear study treatment arm, n (%)	
Arm 1 (BPV 300 mg x 24W w/ LD)	21 (48)
Arm 2 (BPV 300 mg x 12W w/ LD then BPV 150 mg x 12W)	15 (34)
Arm 3 (BPV 300 mg x 12W w/ LD then placebo x 12W)	4 (9)
Arm 4 (placebo x 12W w/o LD then BPV 300 mg x 12W)	4 (9)
Probable duration of chronic HBV infection at B-Clear study baseline, n (%)	
<10 years	11 (25)
≥10–<20 years	14 (32)
≥20 years	19 (43)
HBeAg status at B-Clear study baseline, n (%)	
Negative	34 (77)
Positive	10 (23)
HBsAg category at B-Clear study baseline, n (%)	
>100–≤1000 IU/mL	32 (73)
>1000–≤3000 IU/mL	10 (23)
>3000 IU/mL	2 (5)

*Four non-responders from B-Clear were enrolled into B-Sure; these participants did not meet eligibility criteria but were enrolled in error

- Of the 14 CRs, 10 (71%) discontinued NAs 3 months into B-Sure; of these, 8 (80%) achieved functional cure 6 months post NA cessation and all 8 maintained functional cure up to 18 months (**Figure 2**)
  - Of the 2 participants who did not achieve functional cure at 6 months post NA cessation, 1 had restarted NA therapy by 24 months post NA cessation
- Of the 26 PRs, 22 (85%) discontinued NAs 3 months after rollover into B-Sure; of these, 2 (9%) achieved functional cure and were maintaining functional cure for up to 18 months. Five out of 22 (23%) maintained PR status at 6 months post NA cessation; of these, 2 maintained to 24 months post NA cessation; the 3 losses of PR were due to HBV DNA reversion (**Figure 2**)
  - Among 22 PRs who discontinued NAs, 13 had restarted NA therapy by 24 months post NA cessation

Safety
- After stopping bepirovirsen, there were no safety signals that suggested a latent adverse drug effect following use of bepirovirsen
- AEs of increased ALT were reported in 1 (2%) participant pre-NA cessation (mild severity) and 3 (7%) participants post NA cessation (2 mild, 1 moderate severity)
- Of the 34 participants who discontinued NAs, 5 had ALT ≥2 × ULN
  - One participant who restarted NA therapy had ALT >5 × ULN; no other participants had ALT >5 × ULN

Figure 2: **Participant flow diagram for On-NA participants in B-Sure**



Further consideration of how to handle blips has led to the re-classification of individual participants at the end of the parent study, and therefore the data presented here are different than that previously shared within the abstract. †Four non-responders from B-Clear were enrolled into B-Sure in error but were excluded from the flow diagram; ‡Due to safety. HBsAg reversion, and/or investigator error; §Due to safety of participant and/or investigator discretion based on lab results

Figure 3: **CR participant profiles**

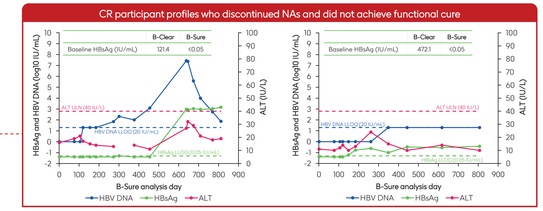
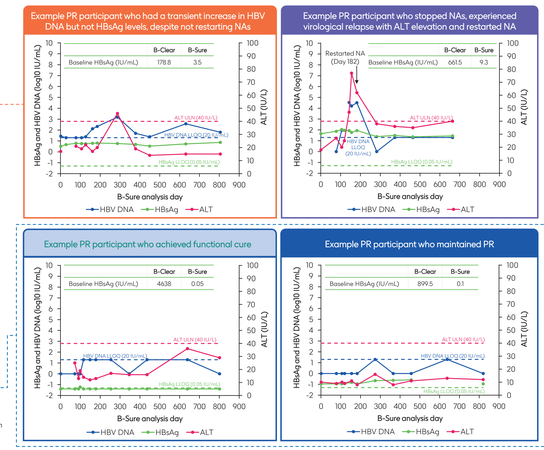


Figure 4: **PR participant profiles**



Conclusions

- This global, long-term follow-up study provides further evidence for the durability of functional cure observed up to 18 months 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 in participants with a PR are being further analysed
- These findings provide evidence of the durability of functional cure observed with bepirovirsen

Abbreviations

AE, adverse event; 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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