Up to 36 months durability of functional cure in response to bepirovirsen therapy in B-Clear Not-on-NA responders: Results from the B-Sure study

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Plain language summary: Bepirovirsen is an experimental medicine for the treatment of chronic hepatitis B infection. In B-Sure, we evaluated the durability of functional cure in response to bepirovirsen treatment. The majority of participants with a complete response achieved functional cure after stopping bepirovirsen, and maintained it up to 36 months

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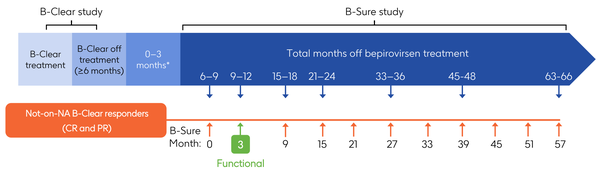
Background

- Functional cure, defined as ≥24 weeks of sustained HBV DNA <LLOQ and HBsAg loss off all HBV treatment, with or without HBsAb[1,2] is the optimal treatment endpoint for chronic HBV infection, but is rarely achieved with NA therapies[2–4]
- Bepirovirsen is an unconjugated antisense oligonucleotide that has been tested in the Phase 3 B-Well studies (NCT05630807, NCT05630820) for the treatment of chronic HBV infection, with the aim of achieving functional cure[5–7]
- In the Phase 2b B-Clear study (NCT04449029), a subset (10%) of participants Not-on-NA achieved a sustained response (undetectable HBsAg [<0.05 IU/mL] and HBV DNA <LLOQ [20 IU/mL]) for 24 weeks after the end of bepirovirsen treatment[5]
- The ongoing Phase 2 B-Sure long-term durability study (NCT04954859) was initiated to generate long-term data on the durability of functional cure in participants with a complete response (CR) or partial response (PR) off bepirovirsen treatment[8]
- Here, we present follow-up data on up to 36 months durability of functional cure for B-Clear Not-on-NA participants who achieved a CR or PR in B-Clear and entered B-Sure
- Data for B-Clear on-NA participants are reported in poster TOP-598

Methods

- The B-Sure study recruited B-Clear Not-on-NA study responders (CR or PR at the end of the B-Clear study) for long-term follow-up
  - CR was defined as maintenance of undetectable HBsAg (<0.05 IU/mL) and HBV DNA <LLOQ (20 IU/mL) for 24 weeks off bepirovirsen treatment in the B-Clear study
  - PR was defined as HBsAg reduction ≥1.0 log_{10} IU/mL compared to B-Clear baseline and maintenance of HBsAg ≥0.05 IU/mL and <100 IU/mL, and HBV DNA <LLOQ for 24 weeks off bepirovirsen treatment in the B-Clear study
- Following entry into B-Sure, Not-on-NA participants were followed as illustrated in **Figure 1**. Participants that maintained at least a PR (defined as HBsAg <100 IU/mL and HBV DNA <LLOQ), at Month 33 in the absence of rescue medication are eligible to continue the study for up to a further 2 years
- This data review has data up to 39 months (indicating up to 36 months durability of functional cure) and a cut-off of 23 September 2025
- Participants were considered to have achieved functional cure if they maintained a CR at Month 3 of B-Sure (i.e. 9 months off bepirovirsen)
- Adverse events were recorded at each visit

Figure 1: **B-Sure study design**



Time between B-Clear end-of-study and entry into B-Sure. Participants could initiate NA treatment if they meet any of the following criteria: a) HBV DNA >20,000 IU/mL; b) HBV DNA >2000 IU/mL after two 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
Arrows denote B-Sure study visits

Results

- In total, 17 Not-on-NA participants (11 with a CR, 5 with a PR and 1 non-responder) were enrolled from B-Clear into B-Sure (**Table 1**)

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 (%)	
<20 years	12 (71)
≥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 participants with a CR, eight (73%) maintained a CR at Month 3, thus achieving functional cure (**Figure 2**). All eight participants maintained functional cure for at least 18 months
  - There were seven participants who maintained functional cure up to 30 months (one participant had not yet reached Month 33). Of these, four maintained functional cure for 36 months (i.e. they had data up to the 39-month visit)
  - Of the three participants who did not achieve functional cure, two experienced HBV DNA and/or HBsAg reversion, without an increase in ALT, one of whom subsequently had virologic relapse. The third participant achieved functional cure at Month 21, then subsequently had HBsAg reversion at Month 33. At their most recent B-Sure visit, they had HBsAg <0.05 IU/mL (HBV DNA remained <LLOQ at all visits; **Figure 3**)
- Of the participants with a PR, 1/5 (20%) maintained a PR at 3 months of B-Sure; this response was maintained to Month 39 of B-Sure (**Figure 2**)
  - Of the participants with a PR, three started NA treatment after B-Sure enrolment, one by Month 15 (**Figure 4**), one by Month 27 and one by Month 33

Safety

- After stopping bepirovirsen, there were no safety signals that suggested a latent adverse drug effect following treatment
- Of all participants, one had 2x ULN ≤ ALT ≤ 5x ULN and one had ALT > 5x ULN

Figure 3: **CR participant profiles**

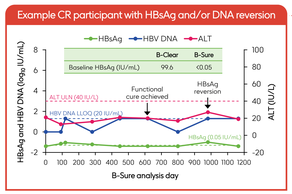
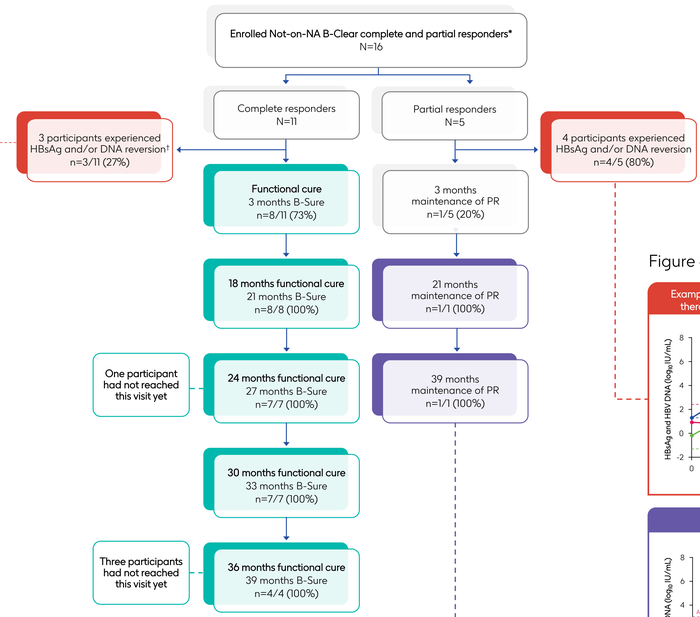
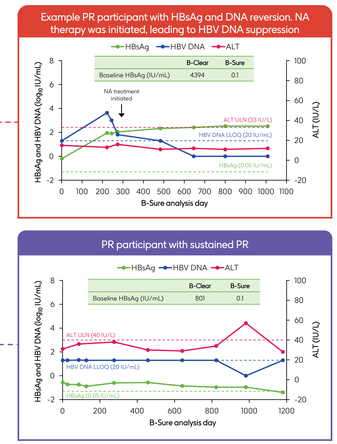


Figure 2: **Flow diagram for Not-on-NA participants in B-Sure**



*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, achieving FC at Month 21, but then had HBsAg reversion at Month 33 (Figure 3)*

Figure 4: **PR participant profiles**



Conclusions

This long-term, global follow-up study provides evidence that functional cure is durable for up to 36 months following the end of bepirovirsen treatment in B-Clear Not-on-NA participants who achieved a complete response in B-Clear

Once achieved, bepirovirsen-mediated functional cure is durable. Two out of 11 participants with a complete response experienced HBsAg and/or HBV DNA reversion, which occurred in the first 3 months of B-Sure

No long-term safety signals were identified during follow-up, and there was no indication of latent adverse effects related to prior bepirovirsen use

Abbreviations

ALT, alanine aminotransferase; BPV, bepirovirsen; CR, complete response; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; IU, international units; 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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Acknowledgements

On behalf of all authors, an audio recording of this poster was prepared by Seng-Gee Lim, who did not receive any payment for this recording. The authors would like to thank the investigators, study centres and personnel, and the GSK B-Sure study team for their work on the B-Sure study, as well as the patients who contributed to the study. The authors would like to thank Matthijs Broer for his authorship on the abstract and his contribution to the study. Editorial support (in the form of writing assistance, including preparation of the draft poster under the direction and guidance of the authors, collating, and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing, and referencing) was provided by Felix Cross, PhD, of Fishawack Indicia Ltd, part of Avalere Health, and was funded by GSK.

Disclosures

This study was funded by GSK (206882). GSK licensed and collaborated on the development of bepirovirsen with Ionis. **S-GL** has consulted for GSK, Gilead, Assembly, Abbott, Roche, Arbutus, Symex, Grifols, Aligos and AusperBio; has delivered sponsored lectures for Symex, Roche, Gilead, GSK and Abbott; and has received grants form Roche and Gilead. **MAr** has delivered sponsored lectures for Gilead Sciences. **SF** has delivered sponsored lectures for Gilead Sciences, MSD and ViiV Healthcare; and has received grants from Gilead Sciences. **TP** has delivered sponsored lectures for Roche, Takeda, DKSH, Viatris, Eisai, AstraZeneca, Sysmex and American Biopharm; and has received grants from Roche Diagnostics, Janssen, VIR, GSK and Sysmex. **OS** has delivered sponsored lectures for Roche Diagnostics and Hepatera. **GR** has consulted for ViiV and Gilead; and has received grants from ViiV and Gilead. **TS** has received grants from GSK and Gilead; and acted as a principal investigator for this clinical trial. **TT** has received grants from GSK. **MT** has delivered sponsored lectures for Gilead Sciences and AbbVie. **MAt**, **NG**, **TK**, **RM**, **QN** and **QX** declared no conflicts of interest. **AW**, **JD**, **LM**, **IS**, **HP**, **YC**, **TL**, **RG**, **MH**, **MP**, **DT** and **RE** are employed by GSK and hold financial equities in GSK. **MP**, **DT** and **RE** are named inventors on pending patent applications for bepirovirsen.

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