Evidence of durable response to bepirovirsen in B-Clear responders: B-Sure first annual report

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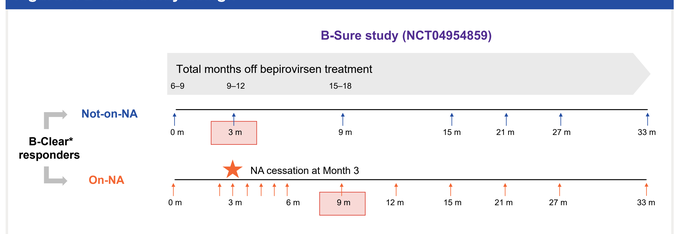
Background and Aims

- Functional cure, defined as the loss of hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA after treatment cessation,[1,2] is rarely (<5%) achieved with current standard of care nucleos(t)ide analogue (NA) therapies.[3–6]
- Bepirovirsen is a novel unconjugated antisense oligonucleotide that targets all HBV RNAs (including pregenomic RNA) and impacts HBV infection in three distinct ways: reductions in viral proteins, including HBsAg, reductions in HBV DNA and stimulation of the immune system.[7–12]
- In the Phase 2b, randomised, B-Clear study (NCT04449029), 32 participants on and not on NA therapy (On-NA and Not-on-NA) achieved a complete response (modified primary endpoint: HBsAg <0.05 IU/mL and HBV DNA level <20 IU/mL [<lower limit of quantification; LLOQ]) maintained for 24 weeks after planned end of bepirovirsen treatment, in the absence of newly initiated antiviral treatment [rescue medication]).[7] The modified endpoint allowed for 'blips' or single timepoint increases above LLOQ in HBsAg or HBV DNA.[7]
- B-Sure (NCT04954859) was initiated to generate long-term data on the durability of response in participants with a complete or partial response after bepirovirsen treatment and included an option for NA cessation for On-NA participants.
- Here we present preliminary data from the first annual review to examine the **durability of treatment response** for B-Clear On-NA and Not-on-NA **complete responders** who enrolled into B-Sure.

Methods

- The B-Sure study recruited responders from the B-Clear study for long-term follow-up (**Figure 1**):
  - Not-on-NA participants will be followed-up at Month 3, Month 9, and every 6 months thereafter for up to 36 months after B-Clear end of study.
  - On-NA participants, if eligible, will cease NA 3 months after entry into B-Sure and be followed more intensively.
- This analysis presents the first annual report from the B-Sure study in B-Clear complete responders (according to the modified primary outcome).

Figure 1. B-Sure study design



*Other parent studies (not included in this analysis) eligible to enter B-Sure include B-Fine (study 212602; NCT04544956) and B-Together (study 209348; NCT04676724). Red box: equivalent to functional cure, all Not-on-NA patients have at least 36 weeks off all treatment (allowing for bepirovirsen wash out), all On-NA participants have at least 24 weeks off NA therapy. m, Month.

- The durability of the response was assessed as follows: **Not-on-NA**: Time from achieving complete response to loss of response; **On-NA**: Time from NA cessation to loss of complete response.
- Adverse events (AEs) were recorded at each visit to assess safety.

Results

- From B-Clear, 13/16 On-NA and 12/16 Not-on-NA complete responders enrolled into B-Sure.
- Most participants were hepatitis B e-antigen (HBeAg) negative and the majority of participants had HBsAg levels ≤1000 IU/mL at baseline (**Table 1**).

Table 1. Baseline demographics and characteristics for On-NA and Not-on-NA populations

Complete responders enrolled into B-Sure	On-NA N=13*	Not-on-NA N=12*
Sex, n (%)		
Male	12 (92)	7 (58)
Age, mean (SD) years	53.20 (10.01)	43.80 (9.96)
B-Clear study treatment arm, n (%)		
Arm 1 (300 mg + LD) x 24W	7 (54)	7 (58)
Arm 2 (300 mg + LD) x 12W + 150 mg x 12W	5 (38)	4 (33)
Arm 3 (300 mg + LD) x 12W + Placebo x 12W	1 (8)	1 (8)
Arm 4 Placebo x 12W + 300 mg x 12W	0	0
HBeAg status at B-Clear study baseline, n (%)		
Negative	10 (77)	12 (100)
Positive	3 (23)	0
HBsAg category at B-Clear study baseline, n (%)		
≤1000 IU/mL	9 (69)	7 (58)
>1000–≤3000 IU/mL	3 (23)	3 (25)
>3000 IU/mL	1 (8)	2 (17)
HBV DNA category at B-Clear study baseline, n (%)		
≤4 $\log_{10}$ IU/mL	N/A	4 (33)
>4–≤6 $\log_{10}$ IU/mL	N/A	7 (58)
>6 $\log_{10}$ IU/mL	N/A	1 (8)

*Two participants each in the On-NA and Not-on-NA populations missed the primary endpoint but were included using the modified primary endpoint due to a HBsAg 'blip' during B-Clear. LD, loading dose; N/A, not available; SD, standard deviation; W, weeks.

Safety:

- There were no safety signals that suggested a latent adverse drug effect following use of bepirovirsen (**Table 2**).

Table 2. Safety profile

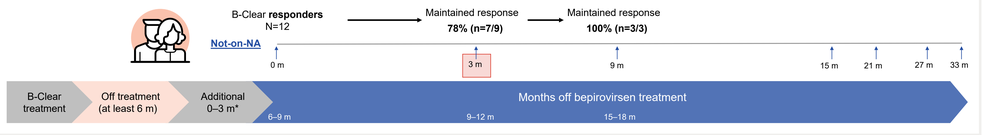
n (%)	On-NA N=13	Not-on-NA N=12
Any AEs	6 (46)	2 (17)
Grade		
Mild	5 (38)	0
Moderate	1 (8)	2 (17)
AEs related to previous treatment in B-Clear	0	0
Any SAEs	0	0

SAEs, serious adverse events.

Not-on-NA population:

- Of the 9 participants with ≥3 months of follow-up within B-Sure, 78% (7/9) maintained response (**Figure 2**). No participant met NA restart criteria.
- Of the 3 participants with ≥9 months of follow-up within B-Sure, 100% (3/3) maintained response (≥15–18 months after end of bepirovirsen).

Figure 2. Responders from the Not-on-NA population maintained durable treatment response off all treatment

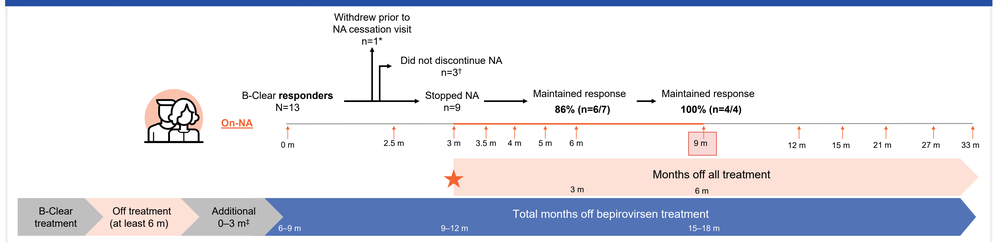


*Mean duration between B-Clear end-of-study and entry into B-Sure: 84 days (range 0–105). Red box: equivalent to functional cure, all Not-on-NA patients have at least 36 weeks off all treatment (allowing for bepirovirsen wash out).

On-NA population:

- 69% (9/13) participants ceased NA as per protocol.
- Of the 7 participants who ceased NA and had ≥6 months of follow-up within B-Sure, 86% (6/7) maintained response 3 months post NA cessation (**Figure 3**).
- Of the 4 participants who ceased NA and had ≥9 months of follow-up within B-Sure, 100% (4/4) maintained response 6 months post NA cessation; no participants restarted NAs.

Figure 3. Responders from the On-NA population maintained durable treatment response off all treatment



*8% (1/13) withdrew prior to NA cessation due to commitments; †23% (3/13) were not eligible to cease NA (2 did not meet protocol defined criteria for cessation due to detectable HBsAg and 1 due to investigator discretion despite HBsAg <0.05 IU/mL) – Eligibility to discontinue NA: HBsAg <0.05 IU/mL and HBV DNA <LLOQ and ALT <1.25 ULN and on stable NA, investigator discretion, evidence of prior or current cirrhosis, or participant preference; ‡Mean duration between B-Clear end-of-study and entry into B-Sure: 102 days (range 94–113). Red box: equivalent to functional cure, all On-NA participants have at least 24 weeks off NA therapy.
ALT, alanine aminotransferase; ULN, upper limit of normal.

Conclusions

- In this global, long-term, follow-up study, 7 participants (n=4 On-NA and n=3 Not-on-NA) demonstrated HBsAg and HBV DNA loss 15–18 months post bepirovirsen cessation.
  - The 4 participants from the **On-NA** population had maintained this response 6 months post NA cessation.
- There were no new safety signals to suggest a latent adverse drug effect following use of bepirovirsen.
- These data provide early evidence on the durability of response observed with bepirovirsen, although they should be interpreted with caution due to low participant numbers. The B-Sure study will continue to evaluate the durability of bepirovirsen response up to 33 months and data will be published when available.

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