Efficacy and Safety of Brelovitug Monotherapy for Chronic Hepatitis D: Primary 24-Week Results from the Phase 3 AZURE-1 Study

Poster 5042

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Introduction

- Chronic hepatitis D (CHD), caused by the hepatitis D virus (HDV), is the most severe form of viral hepatitis, affecting >12 million people worldwide.[1]
- Individuals with CHD have a higher risk of cirrhosis, liver decompensation, and liver cancer, compared to those with chronic hepatitis B (CHB) alone.[2,3]
- HDV depends on hepatitis B surface antigen (HBsAg) for assembly and propagation, providing a rationale for therapeutic strategies that target HBsAg.[4-6]
- Brelovitug (BTG) is an investigational, fully human immunoglobulin G1 (IgG1) monoclonal antibody that targets HBsAg with pan-genotypic activity.[7]
  - Brelovitug potently binds to HBsAg and neutralizes both HDV and HBV, preventing new infection of hepatocytes, and clearing circulating HDV and HBV virions and HBV subviral particles.[7,8]
- The efficacy and safety of brelovitug are being evaluated in the AZURE-1 phase 3 clinical trial.[9]
  - In the AZURE-1 phase 2b trial, brelovitug 300 mg QW and 900 mg Q4W demonstrated higher rates of combined virologic response and ALT normalization versus delayed treatment at Week 24 and was safe and well tolerated.[10]
  - Primary endpoint of combined response at Week 24 is aligned with FDA guidance and reflects both HDV RNA suppression and improvement in hepatic inflammation.[11]

Objective

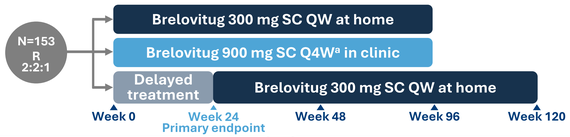
- To evaluate the efficacy and safety of brelovitug compared with delayed treatment at Week 24 in participants with CHD in the AZURE-1 phase 3 trial

Methods

- AZURE-1 (NCT06907290) is a global, randomized, controlled, seamless phase 2b/3 trial of brelovitug vs delayed treatment in participants with CHD that is being conducted across 29 sites in 11 countries, including the United States.[9]
- The phase 3 portion comprises 153 participants.

Key Inclusion Criteria	Key Exclusion Criteria
• Aged ≥18 years • HDV RNA >500 IU/mL and ALT >upper limit of normal (ULN) • Child-Turcotte-Pugh score <7 • Taking or willing to take NA treatment	• Clinical hepatic decompensation • Hepatocellular carcinoma • Presence of other liver diseases • Platelet count <50,000/µL

No exclusion criteria for liver stiffness, portal hypertension, HIV coinfection, bilirubin, albumin, international normalized ratio (INR), or maximum ALT



Primary Endpoint
- Combined virologic response (HDV RNA ≥2 $\log_{10}$ reduction or <LLOQ or TND) and ALT normalization at Week 24

Select Secondary Endpoints
- Safety and tolerability vs delayed treatment
- Efficacy at Week 48 and Week 96
- Change from Baseline in liver stiffness

[a]With a loading dose at Week 2.

Results

Table 1. Demographics and Baseline Characteristics

Parameter[a]	BTG 300 mg QW (n=59)	BTG 900 mg Q4W (n=65)	Delayed BTG Treatment (n=29)	Total (N=153)
Age, years	46.4 (11.6)	45.5 (11.9)	46.3 (13.8)	46.0 (12.1)
Sex, male, n (%)	43 (73)	42 (65)	18 (62)	103 (67)
Race, n (%)[b]				
White	33 (56)	36 (55)	20 (69)	89 (58)
Asian	17 (29)	24 (37)	8 (28)	49 (32)
Black or African American	7 (12)	3 (5)	1 (3)	11 (7)
Other[c]	2 (3)	2 (3)	0	4 (3)
Cirrhosis, n (%)[d]	24 (41)	27 (42)	12 (41)	63 (41)
Child-Turcotte-Pugh score, n (%)[e]				
A5	20 (83)	22 (82)	9 (75)	51 (81)
A6	3 (13)	4 (15)	2 (17)	9 (14)
>A6	1 (4)	0	1 (8)	2 (3)
CSPH, n (%)[f]	11 (19)	13 (20)	7 (24)	31 (20)
Platelet count, n (%)				
<150K/µL	27 (43)	28 (44)	10 (34)	65 (43)
<110K/µL	11 (19)	14 (22)	7 (24)	32 (21)
Liver stiffness, kPa	14.3 (10.8)	13.7 (8.0)	14.6 (11.5)	14.1 (9.8)
Liver stiffness ≥25 kPa, n (%)	8 (14)	7 (11)	5 (17)	20 (13)
ALT, U/L	130 (107)	121 (95)	121 (84)	125 (97)
ALT, U/L ≥5 × ULN, n (%)	12 (20)	11 (17)	5 (17)	28 (19)
HBsAg, $\log_{10}$ IU/mL	3.9 (0.6)	3.9 (0.6)	3.9 (0.5)	3.9 (0.6)
HBeAg+, n (%)	14 (24)	11 (17)	6 (21)	31 (20)
HIV coinfection, n (%)	3 (5)	3 (5)	1 (3)	7 (5)
HDV RNA, $\log_{10}$ IU/mL	5.6 (1.2)	5.6 (1.1)	5.9 (0.8)	5.7 (1.1)
HDV RNA >6 $\log_{10}$ IU/mL, n (%)	32 (54)	24 (37)	14 (48)	70 (46)
HBV genotype, n				
A, B, D, E, N/A[g]	15, 0, 40, 2, 2	6, 1, 56, 0, 2	0, 0, 29, 0, 0	21, 1, 125, 2, 4
HDV genotype, n				
1, 2, 5, N/A[h]	54, 0, 2, 3	61, 1, 1, 2	29, 0, 0, 0	144, 1, 3, 5

[a]Data are mean (SD) unless otherwise indicated. [b]Race was reported by the participant. [c]Includes participants reported as either Native Hawaiian or other Pacific Islander or unknown. [d]Defined as liver stiffness ≥12.5 kPa. [e]Child-Turcotte-Pugh score is n (%) of participants with cirrhosis. [f]CSPH was classified as Yes or Probable according to Baveno VII criteria, on the basis of liver stiffness measured by transient elastography and platelet count. Participants who met neither category are not shown. [g]Includes participants noted as missing, result pending, or unclassified. [h]Includes participants noted as cancelled, missing, or result pending.

AZURE-1 Phase 3 Week 24 Data Met the Primary Endpoint

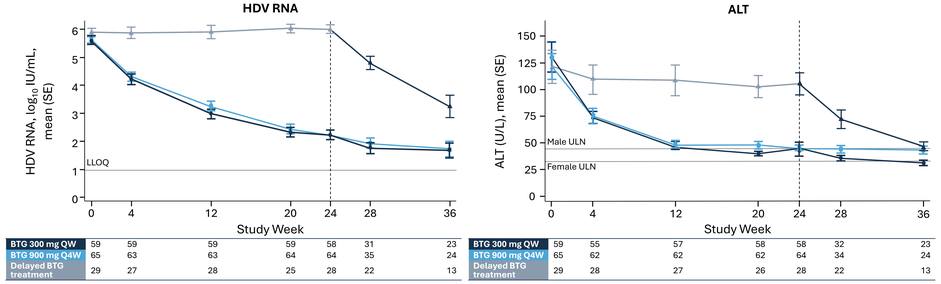
Table 2. Virologic Response and ALT Normalization[a,b]

Parameter, n/N (%)	BTG 300 mg QW (n=59)	BTG 900 mg Q4W (n=65)	Delayed BTG treatment (n=29)
Primary endpoint[c] (Virologic response + ALT normalization)	33/59 (56)[d] ***P*<0.0001**	29/65 (45) ***P*<0.0001**	0/29 (0)
Virologic response (HDV RNA ≥2 $\log_{10}$ reduction or TND)	51/59 (86)	55/65 (85)	0/29 (0)
HDV RNA, LLOQ (<10 IU/mL)	15/59 (25)	17/65 (26)	0/29 (0)
HDV RNA TND	10/59 (17)	11/65 (17)	0/29 (0)
ALT normalization	37/59 (63)	35/65 (54)	0/29 (0)

[a]The full analysis set was defined as participants who were randomized to the BTG 300 mg QW or BTG 900 mg Q4W groups and received brelovitug at least once or were randomized to the delayed BTG treatment group. [b]HDV RNA levels were assessed using an RT-qPCR assay (Victorian Infectious Disease Reference Laboratory, Melbourne) in which LLOQ was 10 IU/mL and limit of detection was 5 IU/mL. [c]*P* values compare each treatment group against delayed BTG treatment using a stratum-adjusted Miettinen and Nurminen method. [d]One participant was HDV RNA TND at Week 20 but was missing Week 24 results due to being out of the country. This participant was considered a nonresponder at Week 24.

Reductions in Both HDV RNA and ALT Levels Were Observed With Brelovitug Treatment

Figure 1. HDV RNA and ALT Levels From Baseline Through Week 36

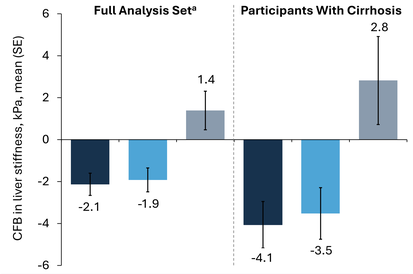


BTG 300 mg QW	59	59	59	59	58	31	23
BTG 900 mg Q4W	65	63	63	64	64	35	24
Delayed BTG treatment	29	27	28	25	28	22	13

BTG 300 mg QW	59	55	57	58	58	32	23
BTG 900 mg Q4W	65	62	62	62	64	34	24
Delayed BTG treatment	29	28	27	26	28	22	13

Improvements in Liver Stiffness Were Observed With Brelovitug Treatment

Figure 2. Change in Liver Stiffness From Baseline at Week 24



BTG 300 mg QW	58	23	
BTG 900 mg Q4W	64	26	
Delayed BTG treatment	28	11	

[a]The full analysis set was defined as participants who were randomized to the BTG 300 mg QW or BTG 900 mg Q4W groups and received brelovitug at least once or were randomized to the delayed BTG treatment group.

Brelovitug Treatment Was Safe and Well Tolerated

Table 3. Summary of Adverse Events

Parameter, n (%)	BTG 300 mg QW (n=59)	BTG 900 mg Q4W (n=65)	Delayed BTG treatment (n=29)
AEs			
Any	27 (46)	40 (62)	8 (28)
Related to treatment	14 (24)	22 (34)	0
AE grade ≥3			
Any	0	0	1 (3)[a]
Related to treatment	0	0	0
Serious AE			
Any	0	0	1 (3)[a]
Related to treatment	0	0	0
AE leading to discontinuation of study drug	0	0	0
Injection site reaction	6 (10)	12 (19)	0
Flu-like illness	3 (5)	7 (11)	0

[a]Grade 4 acute myocardial infarction.

- Both regimens of brelovitug were well tolerated, with no treatment-related SAEs, grade ≥3 AEs, or AEs leading to discontinuation.
- The most common adverse event was injection site reaction; majority were mild in severity.

Conclusions

- In the phase 3 AZURE-1 trial, brelovitug monotherapy administered QW or Q4W, met the primary endpoint at Week 24, demonstrating significant improvements in both HDV RNA and ALT levels compared to delayed treatment in a broad patient population.
- Improvements in liver stiffness were observed at Week 24 in both brelovitug treatment groups.
- Brelovitug was safe and well tolerated, with mild injection-site reactions being the most commonly reported AE.
- AZURE-1 remains ongoing, with additional efficacy and safety assessments planned at Weeks 48 and 96.
- A broader phase 3 program is ongoing (NCT06907290; NCT07200908; NCT07454837; NCT07298330).[9,12-14]

Abbreviations

A5, Child-Turcotte-Pugh A5; A6, Child-Turcotte-Pugh A6; AE, adverse event; ALT, alanine transaminase; BTG, brelovitug; CFB, change from Baseline; CHB, chronic hepatitis B; CHD, chronic hepatitis D; CSPH, clinically significant portal hypertension; HBeAg+, hepatitis B virus e antigen positive; HBsAg, hepatitis B viral surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IgG1, immunoglobulin G1; INR, international normalized ratio; LLOQ, lower limit of quantification; NA, not available; NA, nucleos(t)ide analogue; Q4W, every 4 weeks; QW, once weekly; R, randomized; RNA, ribonucleic acid; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SAE, serious adverse event; SC, subcutaneous; TND, target not detected; ULN, upper limit of normal.

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Disclosures

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