

# HDV Working Group: Summary of Key Discussion Points on Endpoints and Trial Design

**Session III:  
Hepatitis Delta Therapeutics: Clinical Trial Endpoints**



**THE FORUM**

For Collaborative Research<sup>SM</sup>

*Berkeley's Hub for Regulatory Science*



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# Working group objectives



- Review/discuss and recommend endpoints for Hepatitis Delta clinical trials for biological and clinical improvements
  - Context: accumulated data, progress in HDV diagnostics, and new therapies in development.
- Considerations:
  - Chronic suppressive vs finite therapy
  - Diverse mechanism of action of drugs in development
  - HDV RNA in serum vs. liver
  - Liver health biomarkers
  - Patient experience - PROMS

# Why now?

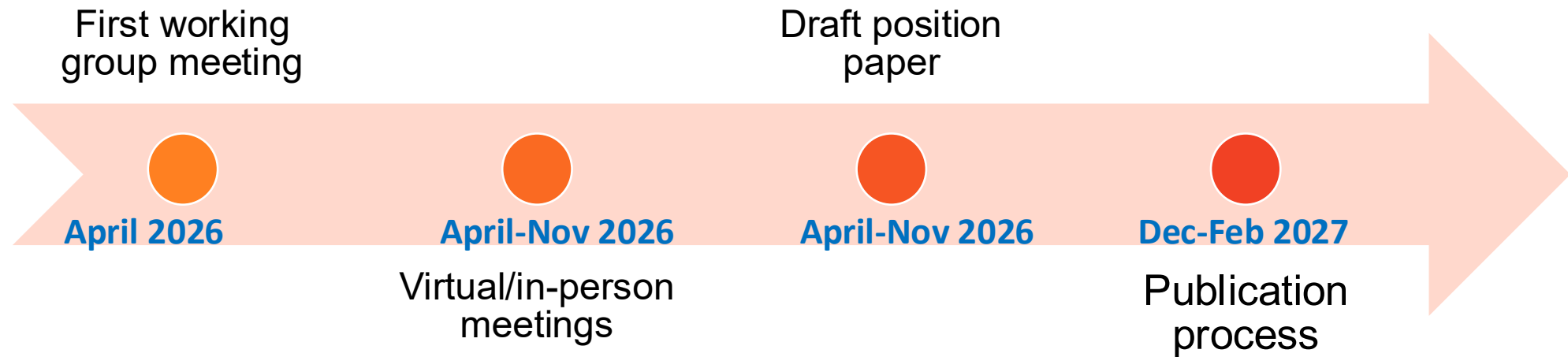
## 2022 →

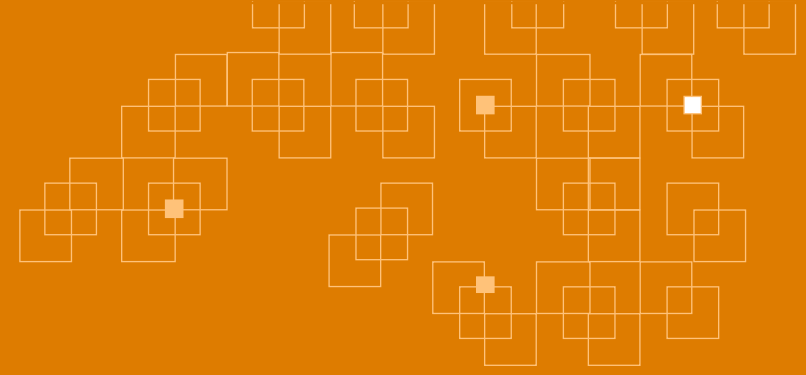
- ≥2 log reduction in HDV RNA + normalization of ALT

## 2026

- 4 yrs bulevirtide RW data
- LREs in BLV-treated patients with cirrhosis
- BLV 10 mg (8.5 mg) approved by FDA (May 22, 2026)
- Long-term interferon data
- Next-generational investigational compounds advancing to phase 3

# Working group timeline





# Key Themes

# Evaluating the combined Endpoint



*Originally established on the basis of historical interferon data and bulevirtide.*

## Equal Weighting?

Scientific basis for weighting virologic and ALT components equally is debated.

## ALT Confounding

Metabolic liver disease may elevate ALT independently of HDV viral activity.

## One-Size-Fits-All?

Same endpoint applied across finite and chronic therapies, and all MOA's may not be appropriate

# Evaluating HDV-RNA TND ± ALT normal as primary endpoint

## The field is moving fast



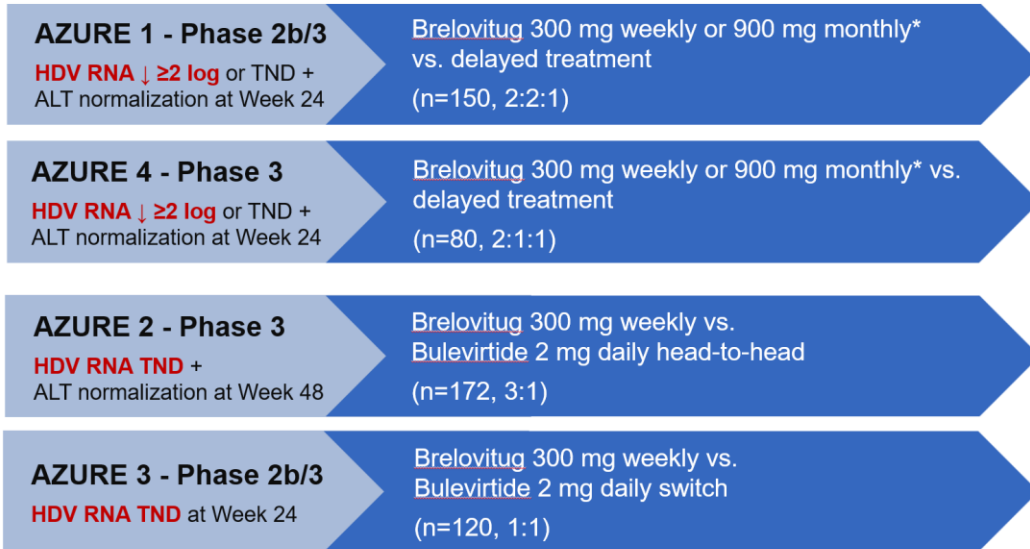
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### Brelivitug (BJT-778 mab) - AZURE Registrational Program

Development supported by:

FDA Breakthrough Therapy Designation

EMA PRIME and Orphan Drug Designation



\*Loading dose administered at Week 2. Brelivitug 300 mg weekly is self-administered by subjects at home. 900 mg monthly is administered in the clinic.  
Note: All studies continue to 96 weeks (or 108-120 weeks for subjects randomized to a treatment delay)

### Tobevibart + Elebsiran in HDV - ECLIPSE Registrational Program

**ECLIPSE 1** Phase 3: tobevibart + elebsiran vs. deferred treatment (n=120, 2:1) *Enrollment Complete*  
HDV RNA TND + ALT normalization at week 48

**ECLIPSE 2** Phase 3: tobevibart + elebsiran vs. bulevirtide switch\* (n=150, 2:1) *Enrollment Ongoing*

Primary Endpoint: **HDV RNA TND at week 24**  
\*Participants who have received BLV 2 mg for ≥ 24 weeks and have

- HDV RNA ≥ 500 IU/mL
- Non-Cirrhotic or Compensated Cirrhotic (CPT-A)
- ALT < 5X ULN
- Platelet count > 60 x 10<sup>3</sup>/μL
- Neutrophils > 1.0 x 10<sup>3</sup>/μL

For more information and a list of trial sites

**ECLIPSE 3** Phase 2b: tobevibart + elebsiran vs. bulevirtide naïve (n=100, 2:1) *Enrollment Complete*  
HDV RNA TND at week 48

HDV, hepatitis D virus; TND, target not detected; ALT, alanine aminotransferase; HDV RNA TND, no detectable HDV RNA

**Does decline of HDVRNA levels always reflect reduction of HDV infected liver cells ?**

# Endpoints and Assay Development

*Endpoints are only as reliable as the tools used to measure them.*



## Roche Diagnostics

HDV RNA assay undergoing validation in the US. Requires demonstration of both undetectable HDV RNA and ALT normalization in line with current guidelines.

## LabCorp Assay

Developed and validated an HDV RNA viral load assay now available on its commercial test menu

## HDV Antigen Detection

HDV antigen faces detection challenges during chronic infection where co-existence of antigen and antibodies creates assay interference.

Assay development requires careful balance between sensitivity and specificity, requiring close collaboration between diagnostic developers and clinical experts.

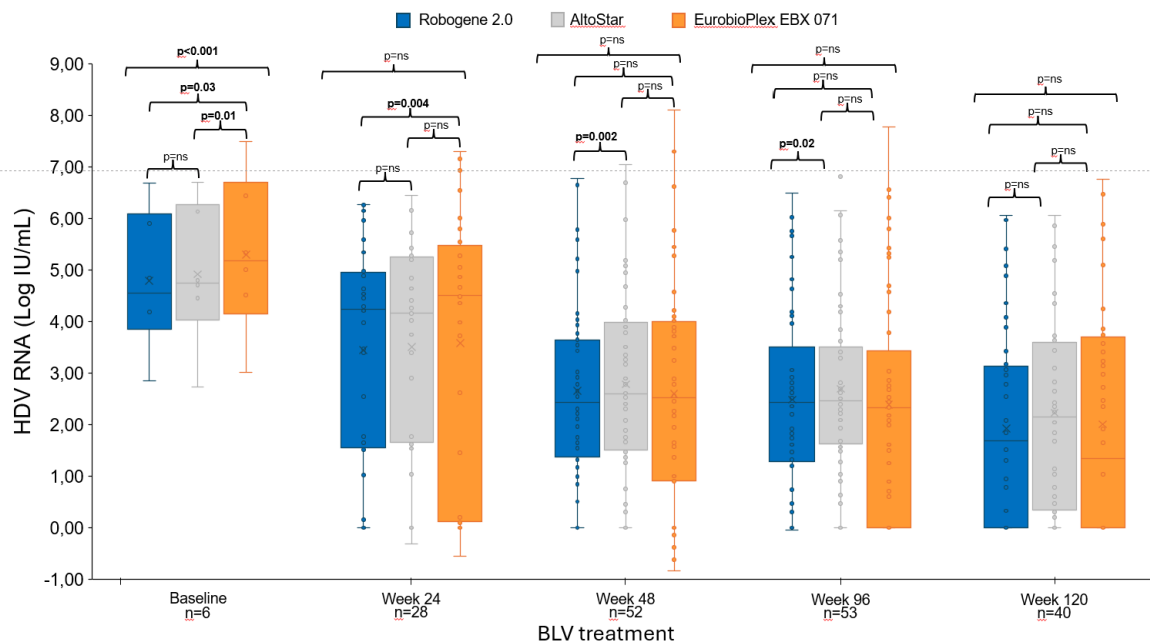
# HDV RNA levels in CHD patients treated with BLV monotherapy

## Comparing performances of the more popular/new assays

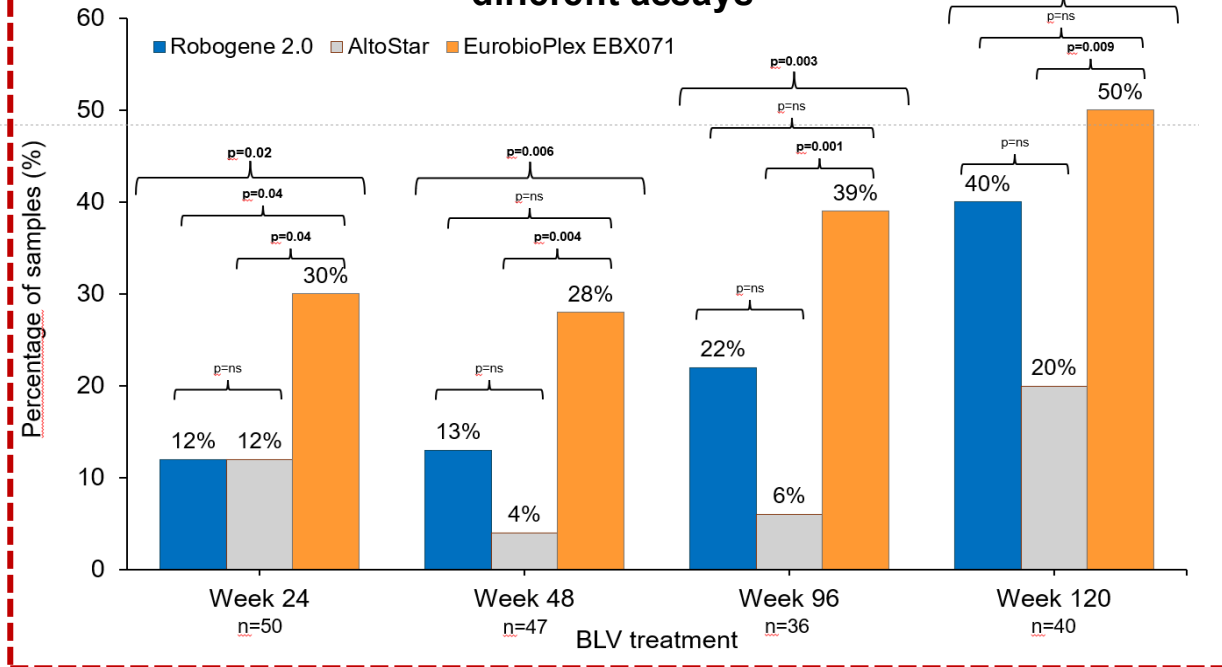


Single center study, frozen samples tested in the same day/lab/technician by different assays  
 600 tests performed: 200 plasma samples collected from 95 CHD (20 untreated and 75 BLV-treated) patients were studied  
 by 3 different assays: Robogene 2.0\*; AltoStar 1.5 and EurobioPlex EBX071 (**new assay**)

HDV RNA levels during BLV therapy by different assays



HDV RNA undetectability rates (TND) during BLV therapy by different assays



**HDV RNA undetectability (TND) rates during BLV monotherapy significantly differed according to the commercial assay used**



\*Manual extraction

# Endpoints and Patient Experience



## Symptom Burden

Severe fatigue is a dominant symptom but not captured by current virologic or biochemical endpoints.

*HBV/HDV co-infected patients face accelerated disease progression and significant psychological burden, yet patient experience is largely absent from current endpoint frameworks.*

## Quality of Life

Health-related QoL instruments should be integrated into endpoint frameworks to capture the lived experience of patients.

# Finite vs. Chronic Therapy

## FINITE THERAPY

### Goal: Sustained off-treatment response (cure)

- Post-treatment endpoint assessment is essential
- Proposed primary timepoint: 6 months after treatment cessation
- Higher virologic bar required — complete suppression or target-not-detected
- Needs predictors to identify candidates likely to achieve durable cure
- Optimal treatment duration and study design remain undefined

## CHRONIC SUPPRESSIVE

### Goal: Long-term viral control and disease prevention

- On-treatment sustained response is the appropriate goal
- Assessment at Week 48 and beyond for durable response
- ALT normalization remains most practical liver health measure
- ALT is the best predictor of long-term liver outcomes vs viral suppression alone
- ALT confounders (metabolic liver disease) must be accounted for

# Additional Endpoints for Consideration

- HBsAg Reduction

For drugs with HBsAg-lowering potential, HBsAg clearance recognized as the ideal endpoint since 2020 but remains difficult to achieve consistently.

But reduction of HBsAg levels does not always reflect decline of HBsAg producing cells in the liver

- Non-invasive Tests (NITs)

Liver stiffness measurement and elastography highlighted as complementary endpoints — can confirm sustained hepatic improvement and track fibrosis over time.

But decline of NITs could be driven, at least in part, by ALT normalization

# Assessing Endpoints: resource limited settings



*Endpoint frameworks can only be meaningfully applied where diagnostics and therapeutics are accessible.*

## **Diagnostic Gap**

Widespread lack of capacity to screen for HDV in Africa. Tests such as antibody screening are not widely available and samples often must be sent off the continent.

## **HDV Hotspots in West and Central Africa**

The true scale of the epidemic remains unknown in the absence of broader screening infrastructure.

## **Equitable Access to Therapies**

Endpoint frameworks can only be meaningfully applied in the African context once equitable access to HDV therapeutics is assured.

## **Population Heterogeneity**

Endpoint design must account for resource-limited settings separately from regions where patients have had prior exposure to multiple treatment modalities.



## Core Regulatory Framework: How does the patient **FEEL · FUNCTION · SURVIVE ?**

### **Biological and Clinical Impact**

Virologic endpoint alone is insufficient for drug approval without accompanying evidence of liver improvement.

### **Bulevirtide Approval Lesson**

The significant number of unknowns in the HDV field was a key factor in the decision to approve bulevirtide based on a combined virological and clinical endpoint.

### **Prevalent Low Response Rates**

Response rates for both approved treatments and drugs in development remain lower than anticipated. This should be carefully considered when proposing any new or additional endpoints.

### **Treatment Modality Considerations**

It may be necessary to propose separate endpoints based on treatment modality, whether finite or chronic.

# Key Questions



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1

What is the primary driver of HDV disease progression and what should the preferred endpoint be?

2

Should the virologic threshold be revised from  $\geq 2$ -log HDV RNA reduction to complete suppression or target-not-detected?

3

Do finite and chronic therapies apply to two distinct patient populations with separate research questions?

4

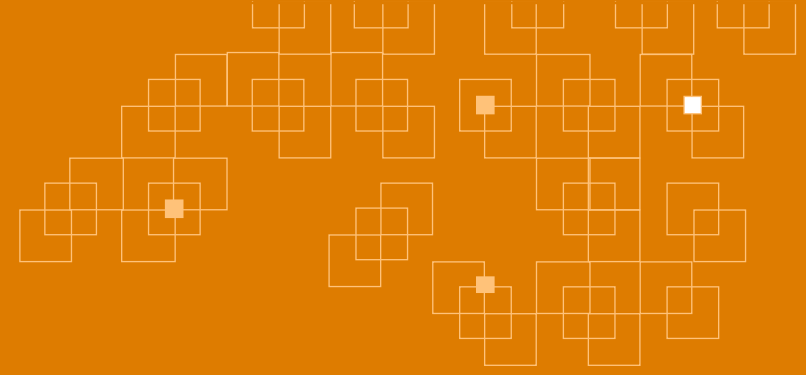
Can predictors be identified to distinguish patients who can achieve durable cure with finite therapy?

5

Should the same endpoint carry the same clinical weight regardless of the drug's mechanism of action?

6

How should ALT data be interpreted in patients with underlying metabolic liver disease?



# Further Discussion