New antivirals for HDV: Phase 2 Studies

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Disclosures:

Advisory/ Speaker Bureau:

Arbutus/ ASC/ Abbvie/ Aligos/Biotest/ Bluejay/ Janssen/ Roche/ DrugFarm/ Gilead/ GSK/ Grifols / PrecisionBio/ Merck/ Tune/ Vir

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Kings ‘guys’ EASL 24

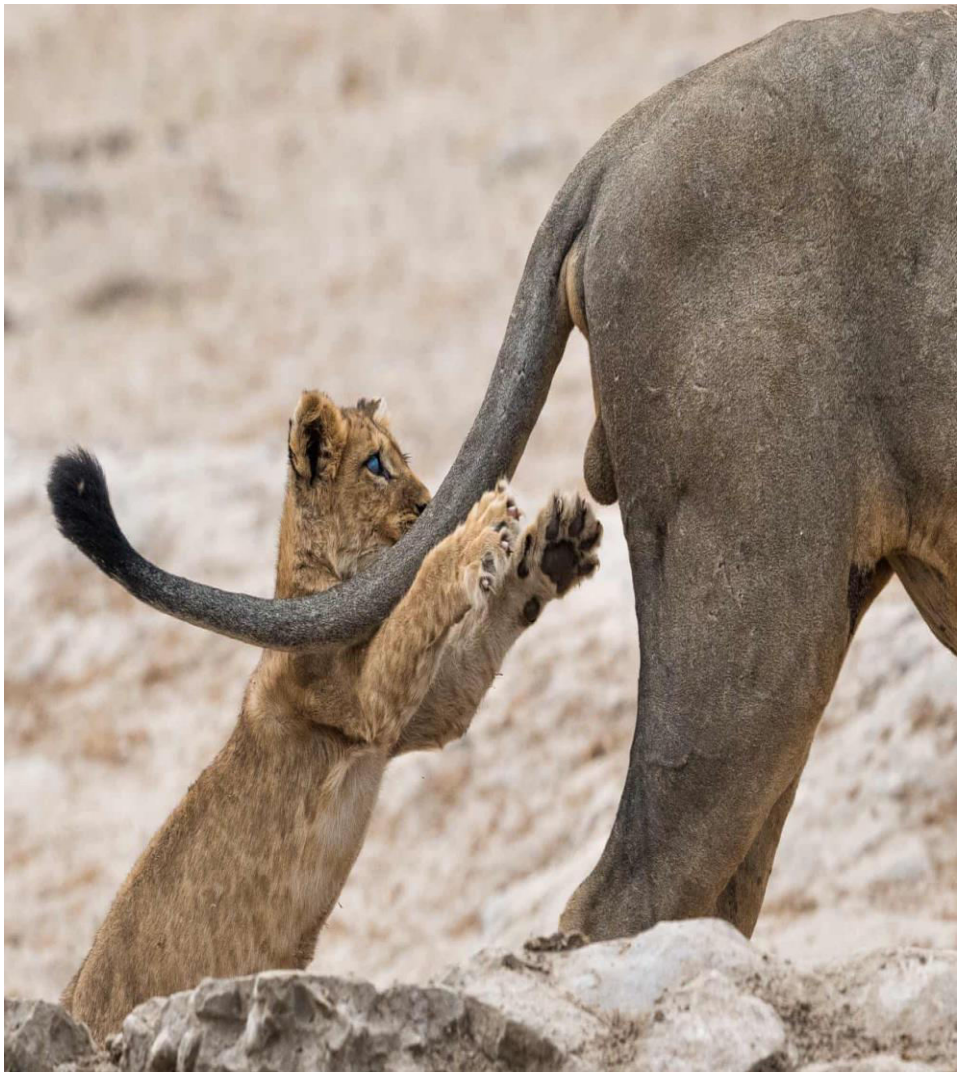
Mission Impossible?

Exciting times…

Well, this is not mission difficult, Mr. Hunt, it's mission impossible. "Difficult" should be a walk in the park for you

Some thoughts

- HDV now seen as a ‘lead-in’ for biopharma
- Recognise the operational logistics
- Heterogeneity
- Assays
- Level of disease - cirrhosis
- Safety – risk *vs* reward
- Need more than chronic suppression
- Small numbers – endpoints (ALT…)



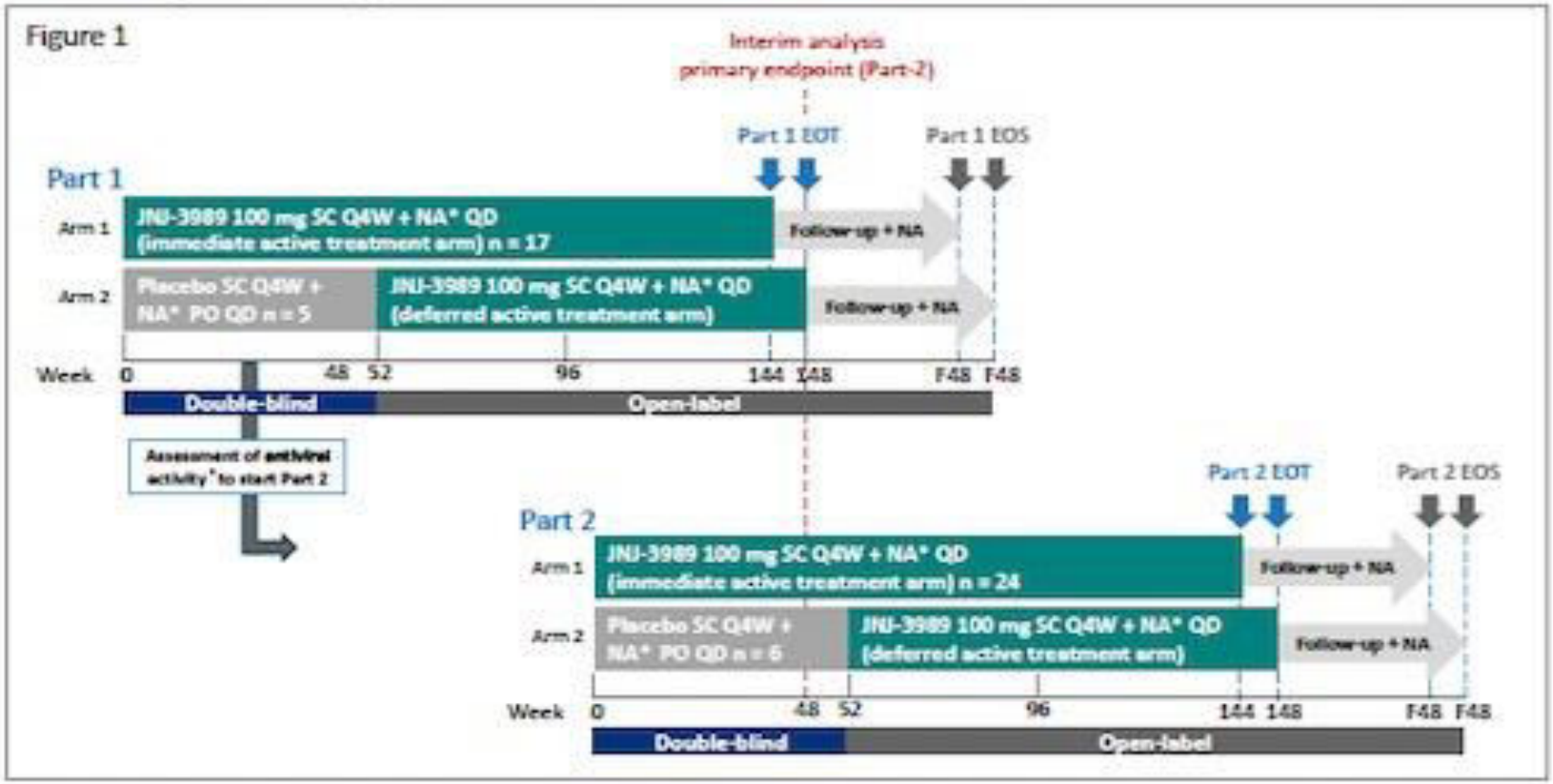
LBP-044

Robust reduction of HBsAg and HDV RNA levels with low risk for ALT elevations in JNJ-73763989 treated patients with chronic hepatitis D (CHD) and baseline HBsAg levels below 10,000 IU/mL: Part 2 of the REEF-D study

Heiner Wedemeyer[1], Pietro Lampertico[2], Edward J. Gane[3], Kosh Agarwal[4], Fehmi Tabak[5], Ulus Akarca[6], Soo Aleman[7], Maria Buti[8], Kathrin Sprinzl[9], Kathleen Donohue[10], John Jerzorwski[11], Thomas Kakuda[12], Thierry Verbinnen[13], Adam Bakala[13], Oliver Lenz[13], Michael Biermer[13]

Study Design

Figure 1



ALT, alanine transaminase; EOS, end of study; EOT, end of treatment; ETV, entecavir; F, follow-up; LLOQ, lower limit of quantification; PO, oral; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TND, <LLOQ target not detected. *ETV/TDF/TAF according to label. †≥8 JNJ-3989-treated patients with ≥0.5 $\log_{10}$ reduction from baseline in HBsAg and HDV RNA and 4 of those with ≥1 $\log_{10}$ reduction in HDV RNA.

Results

Baseline Demographics and Disesase Characteristics

- Baseline characteristics were generally well balanced across the treatment arms.
  - Higher proportion of patients with HBsAg <10,000 IU/mL and HDV RNA <100,000 IU/mL and no cirrhosis in Part 2 (due to adapted inclusion criteria).

Table 1

	Part-1		Part-2		
Characteristic*	Immediate active treatment arm	Deferred active treatment arm	Immediate active treatment arm	Deferred active treatment arm	Total
N	17	5	24	6	52
Demographics					
Male, n (%)	9 (52.9)	2 (40.0)	15 (62.5)	3 (50.0)	29 (55.8)
Age, years	40.9 (10.4)	44.2 (11.9)	43.8 (9.49)	44.8 (11.96)	43.0 (10.11)
White, n (%)	13 (76.5)	4 (80.0)	20 (83.3)	4 (66.7)	41 (78.8)
Disease characteristics					
HBsAg, $\log_{10}$ IU/mL	4.1 (0.5)	3.8 (0.6)	3.63 (0.5)	3.55 (0.5)	3.79 (0.5)
- HBsAg <10,000 IU/mL, n (%)	5 (29.4)	3 (60.0)	16 (66.7)	5 (83.3)	29 (55.6)
HDV RNA, $\log_{10}$ IU/mL	5.1 (1.0)	5.1 (0.9)	4.44 (0.8)	3.90 (0.8)	4.66 (1.0)
- HDV RNA <100,000 IU/mL, n (%)	7 (41.2)	2 (40.0)	19 (79.2)	5 (83.3)	33 (63.5)
HBV DNA <LLOQ, n (%)†	11 (64.7)	5 (100)	19 (79.2)	4 (66.7)	39 (75.0)
ALT, U/L	74.9 (48.0)	95.0 (87.2)	87.8 (56.0)	87.5 (35.3)	84.2 (54.3)
HBeAg positive, n (%)	3 (17.6)	1 (20.0)	2 (8.3)	1 (16.7)	7 (13.5)
NA treatment, n (%)‡	7 (41.2)	3 (60.0)	14 (58.3)	3 (50.0)	27 (51.9)
FibroScan® score ≥12.5 kPa, n (%)	5 (29.4)	1 (20.0)	0 (0)	0 (0)	6 (11.5)

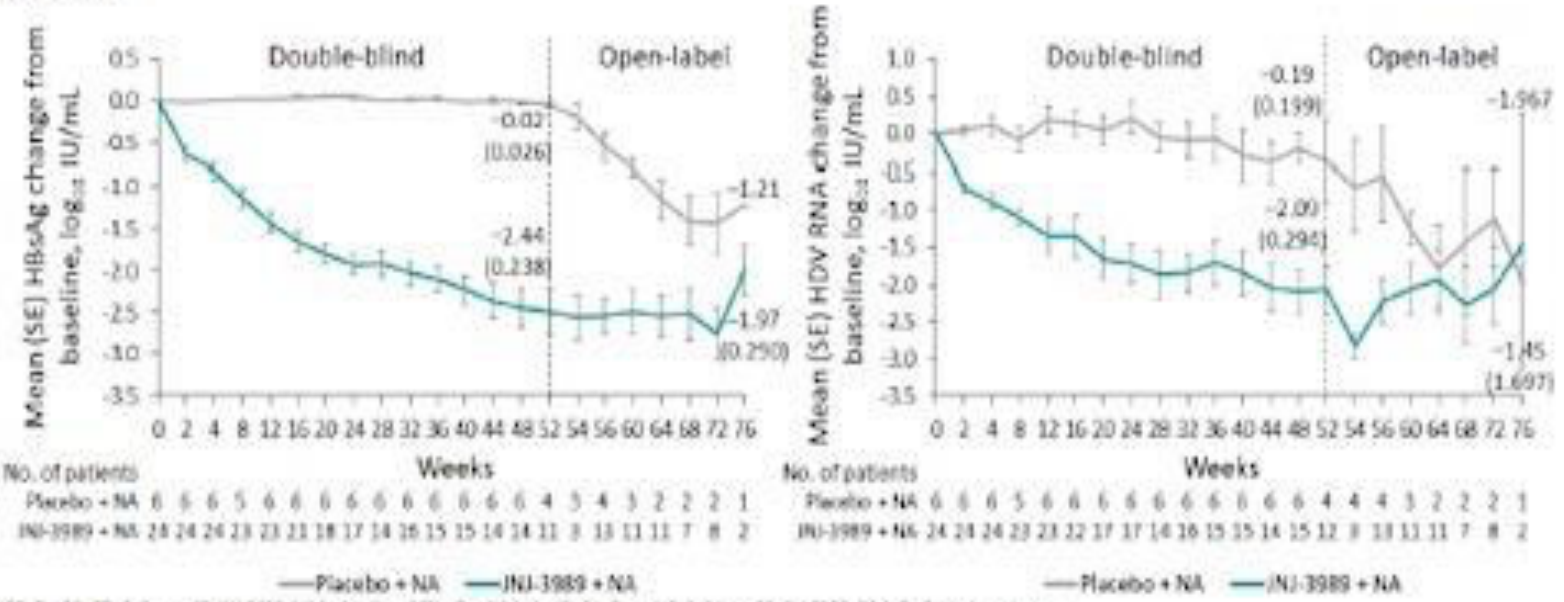
HBeAg, hepatitis B e antigen; SD, standard deviation.
*Mean (SD) unless otherwise noted. †HBV DNA <LLOQ (20 IU/mL). ‡Patients on NA treatment at screening.

HBsAg and HDV RNA (Part 2)

- At week 48, 7/15 (47%) in JNJ-3989+NA and 0/6 (0%) in placebo arm with available week 48 data met primary endpoint of HDV RNA decline from baseline of ≥2 $\log_{10}$ IU/mL (or undetectable) and normal ALT [ITT: 7/24 (29%)].

- Treatment with JNJ-3989+NA led to mean (SE) reduction at week 48 in HBsAg of 2.44 (0.238) $\log_{10}$ IU/mL and in HDV RNA of 2.09 (0.294) $\log_{10}$ IU/mL compared to 0.02 (0.026) $\log_{10}$ IU/mL and 0.19 (0.199) $\log_{10}$ IU/mL with placebo.

Figure 2



DB, Double Blind phase with JNJ-3989+NA in Arm 1 and Placebo+NA in Arm2; OL, Open Label phase with JNJ-3989+NA in both treatment arms

Key efficacy endpoints: Part 1 and 2 combined

- Among all patients who completed 48 weeks of JNJ-3989+NA treatment 41% achieved the primary endpoint (HDV RNA decline ≥ 2log10 IU/mL and ALT normal).
  - Among patients with HBsAg <10 000 IU/mL at screening this was 9/20 (45%).

Table 2

		Normal ALT	HDV RNA ≥2 $\log_{10}$ IU/mL from BL or TND	Combination of both = primary EP	HDV RNA <LLOQ (63 IU/mL)
JNJ-3989 +NA	All patients (ITT)	14/45 (31%)	14/45 (31%)	11/45 (25%)	9/45 (20%)
	Patients with W48 data*	14/27 (52%)	14/27 (52%)	11/27 (41%)	9/27 (33%)
	Patients with W48 data* and HBsAg <10,000 IU/mL†	11/20 (55%)	13/20 (65 %)	9/20 (45%)	7/20 (35%)
Placebo +NA		3/11 (28%)	0/11 (0%)	0/11 (0%)	0/11 (0%)

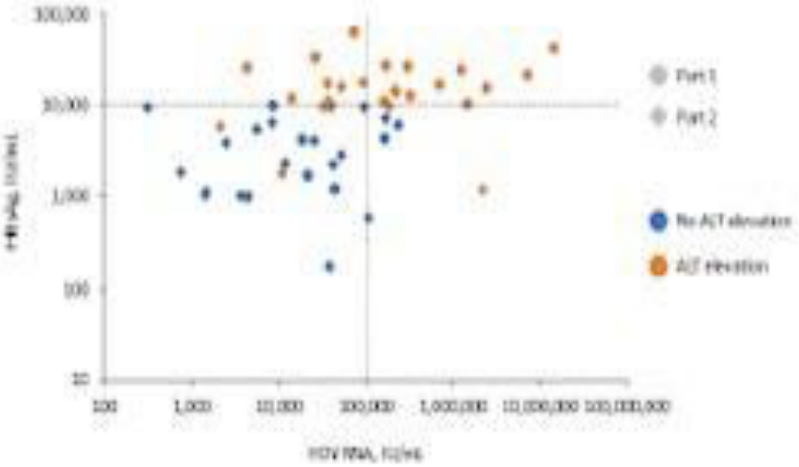
*Four Part-1 placebo patients who rolled over at w52 were counted once for placebo (W0-48) and again for JNJ-3989 (W52-100); † assessed at screening.

Predictors of ALT flare: Part 1and 2 combined

- Screening HBsAg levels showed the best association with JNJ-3989 on-treatment ALT flares
  - Among 24 patients with HBsAg <10,000 IU/mL at screening 24 (82.8%) had no ALT elevation while all 19 (100%) with HBsAg ≥ 10,000 IU/mL had ALT elevation

Table 3 / Figure 5

	n*	At Scr/BL	n	ALT elevation	No ALT elevation
HBsAg IU/mL	48	<10,000	29	5 (17.2%)	24 (82.8%)
		≥10,000	19	19 (100%)	0
HDV RNA IU/mL	48	<100,000	31	11 (35.5%)	20 (64.5%)
		≥100,000	17	13 (76.5%)	4 (23.5%)
HBcrAg log U/mL	47*	<4	24	6 (25%)	18 (75%)
		≥4	23	17 (74%)	6 (26%)



*Includes 48 participants who received >4 weeks of JNJ-3989 in either arm. †HBcrAg baseline value is missing in one participant.

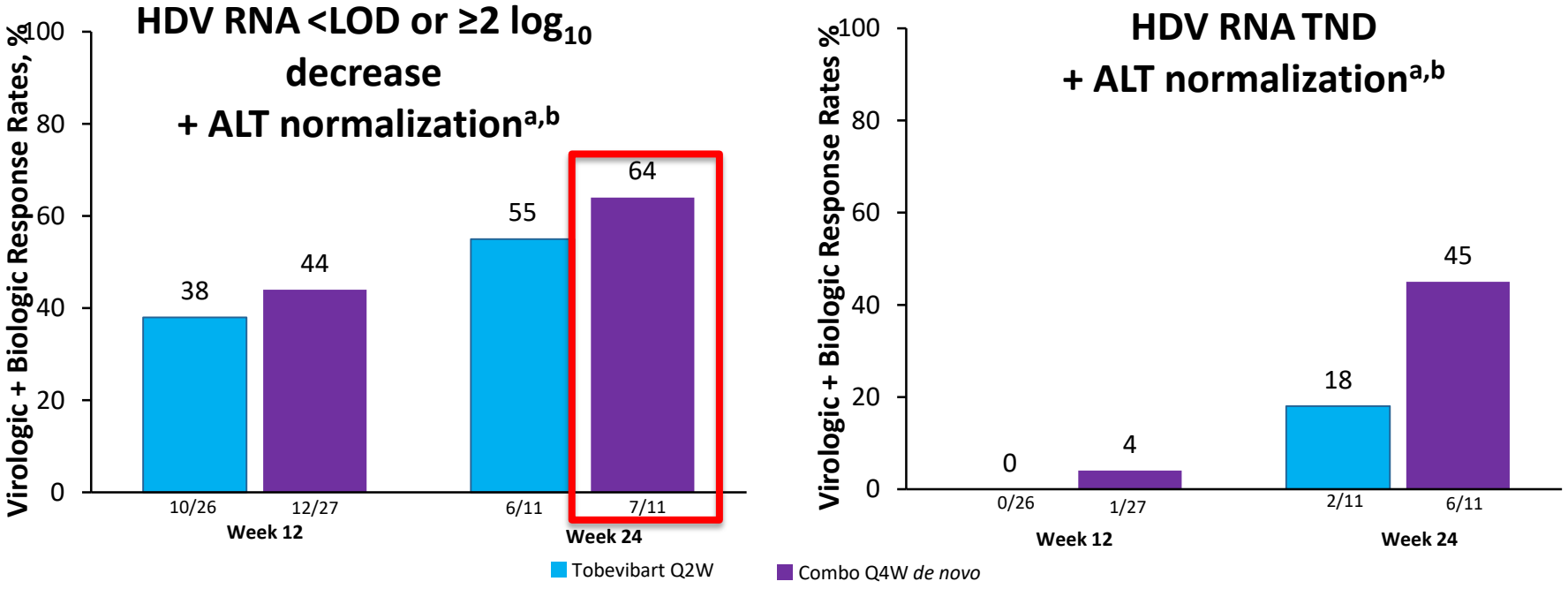
SOLSTICE Study Endpoints

- **Primary Endpoints:**
  - –Virologic and ALT response at Week 24
    - Virologic response = HDV RNA <limit of detection (LOD; 14 IU/mL) or ≥2 $\log_{10}$ IU/mL decrease from baseline
    - ALT response = alanine aminotransferase (ALT) <upper limit of normal (ULN; female = 33 IU/L; male = 40 IU/L)
  - –Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- **Selected Secondary Endpoints:**
  - –HDV RNA < LLOQ
  - –HDV RNA < LOD
  - –HDV Target Not Detected (TND)

SOLSTICE ClinicalTrials.gov Identifier: NCT05461170.
HDV, hepatitis D virus.

Asselah T et al 2024

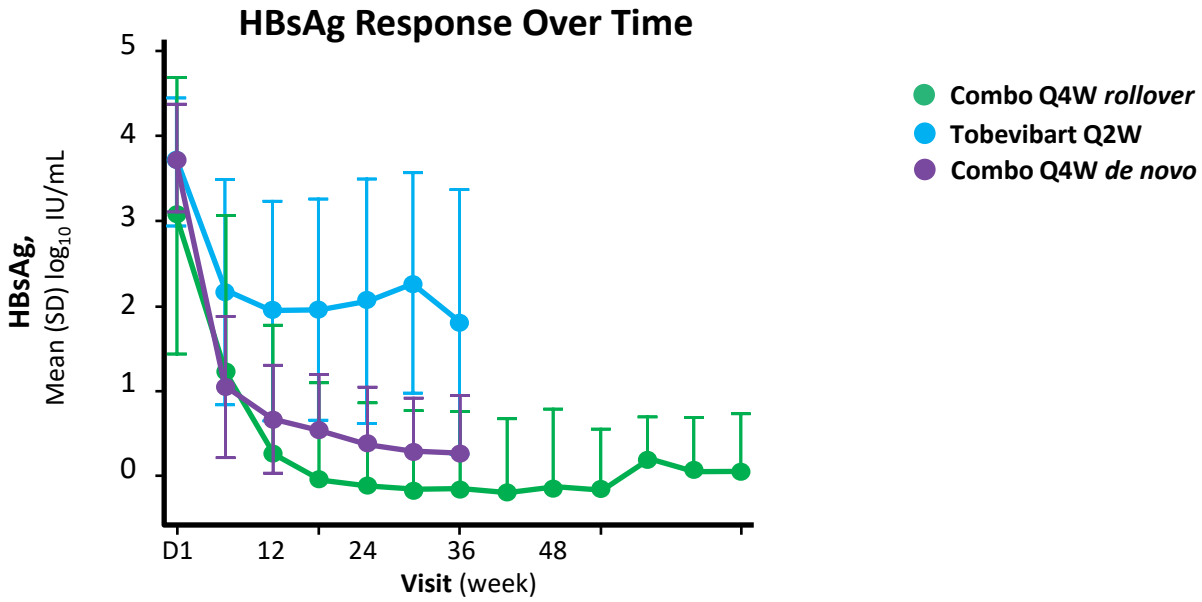
Tobevibart Q2W and Tobevibart + Elebsiran (Combo *de novo*): Combined Response Rates (Preliminary Data)



Tobevibart: 26/33 (79%) and 11/33 (33%) of participants reached Weeks 12 and 24, respectively
Tobevibart + elebsiran: 27/32 (84%) and 11/33 (33%) of participants reached Weeks 12 and 24, respectively

ALT, alanine aminotransferase; combo, combination; F, female; HDV, hepatitis D virus; LLOQ, lower limit of quantification; LOD, limit of detection; M, male; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TND, target not detected; ULN, upper limit of normal.
[a]Robogene® 2.0 assay (Roboscreen GmbH) was used to assess HDV RNA, analyzed by Viroclinics-DDL™. LOD = 14 IU/mL; LLOQ = 63 IU/mL.
[b]ALT ULN M = 40 IU/mL; ALT ULN F = 33 IU/mL.

Tobevibart Q2W and Tobevibart + Elebsiran (Combo) Cohorts: HBsAg Responses



	Combo Q4W *rollover*			Tobevibart Q2W		Combo Q4W *de novo*	
	Week 12 N = 6[a]	Week 24 N = 6[a]	Week 48 N = 5[a]	Week 12 N = 25[a]	Week 24 N = 9[a]	Week 12 N = 29[a]	Week 24 N = 14[a]
Δ HBsAg relative to Day 1 (mean ± SD),[b] log_{10} IU/mL	–3.1 ± 1.0	–3.2 ± 0.9	–3.5 ± 0.8	–1.7 ± 0.8	–1.8 ± 0.9	–3.2 ± 0.5	–3.3 ± 0.5

Combo, combination; D, day; HBsAg, hepatitis B virus surface antigen; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SD, standard deviation.
[a]N is the number of participants who have completed the study visit or discontinued before the study visit.
[b]Combo Q4W *rollover* D1 = Day 1 of combo therapy.

Rapid Reductions of HDV RNA and ALT with the Monoclonal Antibody, BJT-778: Results from a Phase 2 Study

Kosh Agarwal[1], Marta Dobryanska[2], Alina Jucov[3], Patrick Kennedy[4], Edward J. Gane[5], Man-FungYuen[6], Grace Lai-Hung Wong[7], Simone Strasser[8], Jacinta Holmes[9], Stuart Roberts[10], Hassan Javanbakht[11], Nancy Shulman[11]

BJT-778 has Multiple Modes of Action

BJT-778 300 mg SC once weekly for 48 weeks, n=10-20

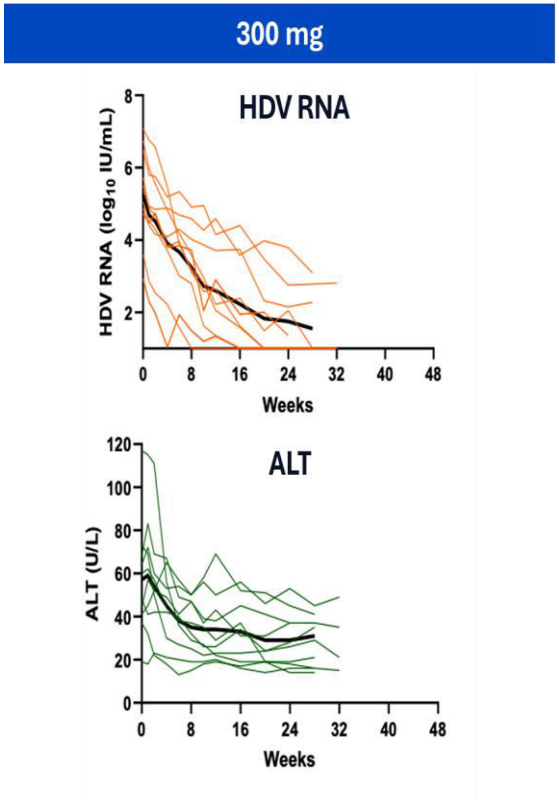
BJT-778 600 mg SC once weekly x 12 weeks, then every other week x 36 weeks, n=10-20

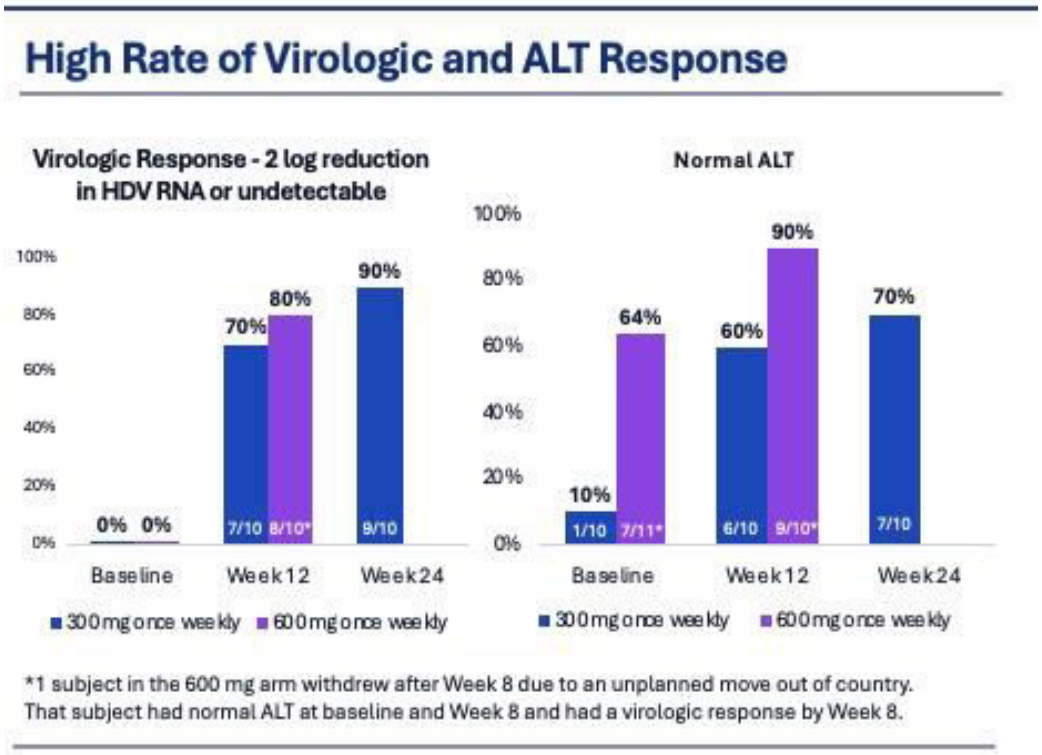
BJT-778 900 mg SC every other week x 4 weeks, then every 4 weeks for 44 weeks, n=10-20

- Chronic HDV
- HBV DNA <100 IU/mL on NUCs
- Quantifiable HDV
- HBsAg >10 IU/mL
- Compensated liver disease
- PLT >100 K/mm^3
- ALT ≤ 10x ULN
- Well-controlled HIV OK

Agarwal K, et al. EASL 2024 LBP-001

Rapid declines in HDV RNA and ALT with BJT-778 anti-HBs mAb treatment





	Week 24
Virologic Response	9/10 (**90%**)**
HDV RNA <10 IU/ml (BLQ)	5/10 (**50%**)***
ALT normalization*	6/9 (**67%**)
Combined response*	6/9 (**67%**)

*In subjects with abnormal ALT at baseline
The remaining subject responded at Week 28 **(100%)
***An additional subject became <10 IU/mL at Week 28 **(60%)**

Agarwal K, et al. EASL 2024 LBP-001

Adverse Events

Subjects, n (%)	300 mg QW N=10	600 mg QW N=11	900 mg 0, 2, 4 wks then Q4W N=10
any AE	5 (50%)	9 (82%)	2 (20%)
any AE related to treatment	2 (20%)*	7 (64%)**	2 (20%)***
AEs leading to discontinuation	0	0	0
Grade 3 or 4 AEs	0	0	0
SAEs	0	0	0

* Injection site erythema; pyrexia

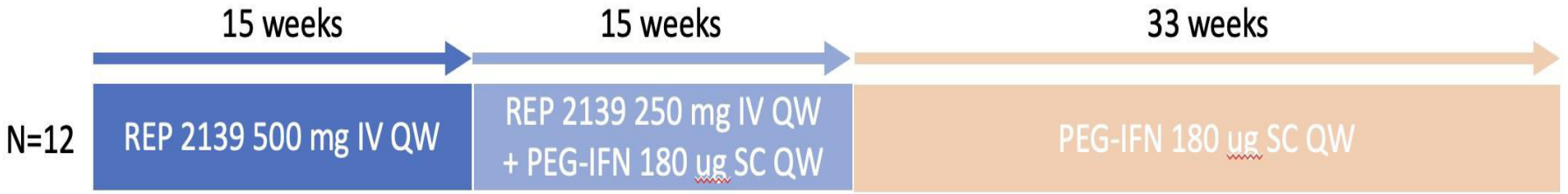
**Injection site erythema (5), injection site pruritus, injection site swelling; pyrexia; abdominal pain; arthralgia; influenza-like illness

***Headache, pyrexia, pain in extremity; Influenza-like illness

- BJT-778 was safe and well tolerated
- No Grade 3 or 4 AEs, SAEs, or discontinuations due to AEs have been observed. The most common events were Grade 1 injection site events.

REP 2139 in HDV patients: phase II clinical trial data

Study REP 301: HDV patients, non-cirrhotics, HBeAg negative



	REP 2139 monotherapy	End of combination therapy	End of treatment
HBsAg reduction (log from baseline)	3·31 (1·99)	4·15 (2·24)	3·45 (2·70)
HBsAg negative*	2 (17%)	4 (33%)	5 (42%)
Anti-HBs positive†	5 (42%)	6 (50%)	6 (50%)
HDV RNA reduction (log from baseline)	4·21 (1·99)	5·68 (1·14)	5·34 (2·34)
HDV RNA negative‡	4 (33%)	10 (83%)	9 (75%)

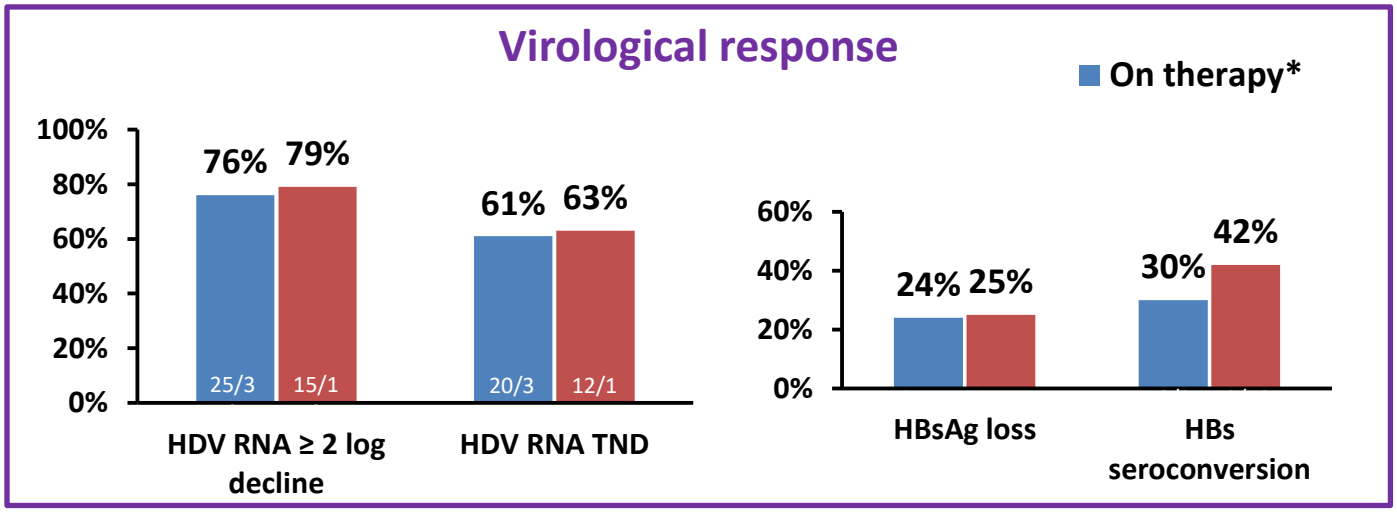
Long-term follow-up study up to 7.4 years:

- 64% (7/11) HDV RNA undetectable
- 4 (36%) with HBsAg loss (HBV functional cure)

Compassionate use of REP 2139-Mg in hepatitis D patients with advanced liver disease

REP 2139 is a nucleic acid polymer (NAP) with dual functions:
Inhibits HBsAg subviral particle assembly in the secretory pathway (via binding to DNAJB12)
Inhibits HDV RNA replication / morphogenesis in the nucleus by binding to HDAg

33 HDV patients with compensated / decompensated cirrhosis and failure during pegIFN ± BLV were treated with REP 2139-Mg SC QW + TDF (or TAF) PO QD ± pegIFN SC QW for a planned duration of 48 weeks



Removal of all therapy in three patients: all with HDV TND and HBV functional cure

4 patients are still on treatment

Primary AE are ALT flares:
Asymptomatic and self-resolving (mainly with pegIFN) but lower in intensity and prevalence than observed in prior clinical trials

Permission C Stern

final thoughts

- Encourage smarter protocols with more stringent end-points
- Diversity *vs* site capability
- BLV experienced….
- Translational elements critical
- Finite therapy
- We need to be more agnostic re paradigm (immune assets)
- ASOs + ?

Accept that some days you are the bird and some days you are the buffalo… (KA™☐)

HBV vs HDV