ABSTRACT #927

A PHASE 2 RANDOMIZED CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF PEGYLATED INTERFERON LAMBDA MONOTHERAPY IN PATIENTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION: INTERIM RESULTS FROM THE LIMT HDV STUDY

S. Hamid[1*], O. Etzion[2*], Y. Lurie[3], N. Bader[1], David Yardeni[2], S. M. Channa[4], M. Mawani[1], O. Parkash[1], E. B. Martins, E. J. Gane[5]

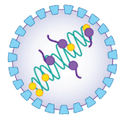
1. Aga Khan University and Hospital, Karachi, Pakistan; 2. Gastroenterology and Liver Disease Institute, Soroka University Medical Center, Beer-Sheva, Israel ; 3. Shaare Zedek Medical Center, Jerusalem, Israel;
4. Department of Gastroenterology, Ghulam Muhammad Mahar Medical College, Sukkur, Pakistan; 5. Auckland City Hospital, Auckland, New Zealand
*These authors share lead authorship

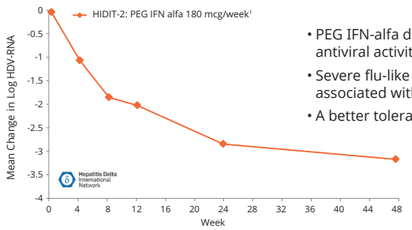
1 ABSTRACT

Background and Aims: Globally 15-20 million people are coinfected with hepatitis delta (HDV) and hepatitis B (HBV) viruses. Interferon (IFN) or pegylated (PEG) IFN-alfa have been tested in patients with chronic HDV (CHD). Up to 25% of patients may become HDV PCR-negative, but most relapse after therapy is discontinued and the tolerability profile is unsatisfactory. PEG IFN lambda-1a (Lambda) is a Type III IFN. Based on Lambda's more limited receptor distribution and previous data from HBV and HCV studies, it is postulated that Lambda could induce HDV responses, but with fewer side effects than IFN-alfa. LIMT HDV is the first study of Lambda in patients with CHD infection, including cirrhotics. Methods: Randomized, open-label study of Lambda 120 or 180 µg subcutaneous injections administered weekly for 48 weeks in patients with chronic HDV. Major inclusion criteria were: positive HDV RNA by qPCR, elevated ALT<10xULN, compensated liver disease and platelets ≥90,000 cells/µL. HDV RNA (Robogene 2.0, LLOQ 14 IU/mL), ALT, bilirubin and other parameters were assessed at each visit. Tenofovir or entecavir were started at baseline (BL) and will continue through the end of the study. Results: To date, 20 patients (15 male, 7 cirrhotic), median age 35 (20-54), have been enrolled; eight randomized to Lambda 180 µg/week and 12 to 120 µg/week. At BL, mean lab values were: HDV RNA 4.5 log10 IU/mL (SD ±1.36); ALT 104 IU/mL (47-364 IU/mL) and bilirubin 13 µmol/L (3-20 µmol/L). Mean Fibroscan score was 11.8 kPA (4.6-27.4 kPA). To date, 13 and 11 patients have reached Weeks 4 and 8 of therapy, respectively. At Week 4, 3/13 (23%) patients had HDV RNA < LLOQ, one of which was PCR-negative. At Week 8, 6/11 (55%) had HDV RNA < LLOQ, 3 of which were PCR negative. HDV RNA drop from BL>2 log_{10} was observed in 31% (4/13) and 46% (5/11) of patients at Weeks 4 and 8, respectively. Three patients had grade 3 elevations of ALT. Three patients developed jaundice (two on 180 µg/week and one on 120 µg); two of which required permanent drug discontinuation, and one required temporary drug interruption and resumption at a reduced dose (peak direct bilirubin 86, 465 and 36 µmol/L, respectively). In all cases, jaundice was preceded by a rise in GGT. Constitutional symptoms were less frequent and milder than historical data with PEG IFN-alfa. Conclusions: This interim analysis indicates that weekly Lambda – 120 µg or 180 µg – has antiviral activity against HDV, with some patients already becoming PCR-negative by Week 8 of therapy. Overall, Lambda was well-tolerated, and hyperbilirubinemia events in three patients responded to dose reduction or discontinuation. Week 24 data is presented.

2 ABOUT HDV

- Most severe form of human viral hepatitis
- Always associated with HBV infection
- HDV causes more rapid disease progression
  - Compared to HBV mono-infection
- No FDA approved Rx
- 15-20 M HDV infected patients worldwide
- 4-6% of HBV infected patients are coinfected with HDV

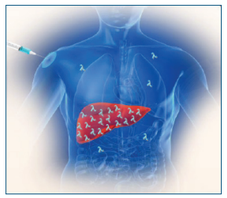




- PEG IFN-alfa demonstrates antiviral activity in HDV patients
- Severe flu-like symptoms are associated with PEG IFN-alfa
- A better tolerated IFN is needed

3 ABOUT PEGYLATED INTERFERON LAMBDA

- A novel first in class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Greater than 3,000 patients in 17 clinical trials (HCV / HBV) have been dosed with IFN lambda
- Antiviral activity with less of the typical IFN alfa related side effects[2]



Limited Extra-Hepatic Lambda Receptor Distribution

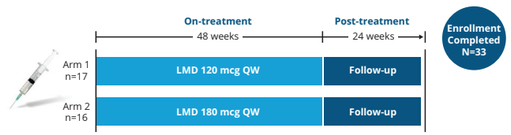
Potential for LESS IFN-associated abnormalities:

- ↓ Neutropenia
- ↓ Thrombocytopenia
- ↓ Flu-like Symptoms
- ↓ Musculoskeletal Symptoms

4 LIMT HDV STUDY

Lambda Interferon Mono Therapy Study in HDV

- Randomized, open-label study of Lambda 120 or 180 mcg subcutaneous (SC) injection weekly for 48 weeks in patients with chronic HDV infection.



5 LIMT HDV STUDY

Objectives

- Evaluate safety, tolerability and efficacy
- Evaluate the proportion of patients with undetectable HDV RNA:
  - 12 weeks after the end of treatment
  - 24 weeks after the end of treatment

Study Sites

- Auckland, New Zealand (N=4)
- Karachi, Pakistan (N=15)
- Beersheba, Israel (N=11)
- Jerusalem, Israel (N=3)

33 Patients Randomized

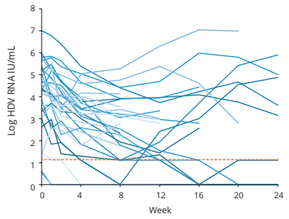
6 PATIENT BASELINE CHARACTERISTICS

Characteristic	Values
N	33
Age, years (range)	36* (20, 63)
Male, n (%) – White – Black – Pacific Islander – Other	 13 (39.4%) 1 (3.0%) 4 (12.1%) 15 (45.5%)
BMI, kg/m² (range)	24.7* (14.0, 37.1)
HDV-RNA, log_{10} IU/mL (range)	4.4* (2.4, 5.9)
ALT, U/mL (range)	84* (35, 364)
Albumin, g/dL (range)	4.4* (3.7, 5.2)
INR	1.2* (1.0, 1.5)
Platelets, x10^9/L (range)	170* (95, 281)
Bilirubin, mg/dL (range)	0.5* (0.2, 1.2)

[1] *Normal range for ALT = 10 – 35 U/mL (female); 10 – 50 U/mL (male)*
[2] *Normal range for bilirubin = 0 - 1.2 mg/dL*
[3] *Median Values*

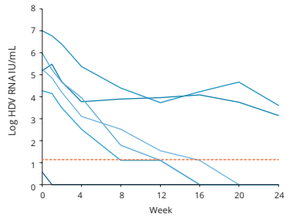
7 LIMT HDV STUDY: INTERIM ANALYSIS

All Patients at Time of Analysis (N=33)



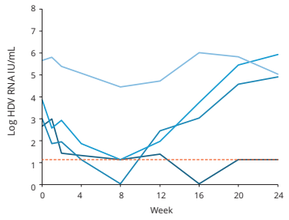
Week	N	≥ 2 log decline	PCR-negative
4	33	7 (21.2%)	3 (9.1%)
8	32	12 (36.4%)	5 (15.6%)
12	23	9 (39.1%)	4 (17.4%)
24	10	5 (50.0%)	4 (40.0%)

Responders: 6 of 10 (60%) Patients at Week 24



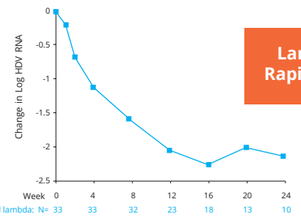
- 10 of 33 patients reached Week 24 at time of analysis
- 6 of 10 (60.0%) patients achieve ≥ 2 log decline or HDV PCR-negativity

Nonresponders / Rebounders By Week 24



- 3 of 10 (30.0%) patients demonstrate > 1 log on-treatment rebound
- 1 of 10 (10.0%) patients < 1 log decline

Mean Change in HDV RNA



Lambda Demonstrates Rapid Decline in HDV RNA

8 SAFETY

Lambda Safety at Time of Analysis

Event	LIMT HDV (N=33)
SAEs	5 (15%)[a]
Discontinuations due to AEs	5 (15%)
ALT increase (>5x ULN)	18 (55%)
AST increase (>5x ULN)	10 (30%)
Hyperbilirubinemia (>2.5x ULN)	3 (9%)[b]
ALT Flare[c]	4 (12%)
Dose reductions	4 (12%)
Dose interruptions	4 (12%)

[a] 7 SAEs occurring in 5 patients; [b] 1 patient had elevated bili at baseline; [c] ALT > 2x BL and 10x ULN

AE of Special Interest	% Patients Reporting	Lambda 120/180 mcg N=33			
		Grade			
		1	2	3	4
Pyrexia[a,b]	13 (39.4%)	11	2		
Alopecia[a]	0 (0%)				
Fatigue[a]	11 (33.3%)	9	2		
Headache[a,b]	21 (63.6%)	15	6		
Neutropenia[a]	1 (3%)				1
Thrombocytopenia	0 (0%)				
Myalgia[a,b]	11 (33.3%)	8	3		
Dizziness[a,b]	4 (12.1%)	3	1		
Pruritus[a]	3 (9.1%)	3			
ALT increase	6 (18.2%)		6		
Depression[b]	1 (3%)	1			
Influenza-like Illness[b]	4 (12.1%)	4			

[a] AEs occurring in >15% in alfa cohorts from prior studies: Chan et al, J Hepatology, 2016
[b] Preferred terms found in the alfa label reported in at least 5% of patients

9 DISCUSSION

- At Week 24 of treatment (time of analysis):
  - 10 of 33 patients show Mean HDV RNA decline of 2.0 logs
  - 50% patients achieve ≥ 2 log decline in HDV RNA
  - 40% patients are HDV PCR-negative
- Mild to moderate headache, pyrexia, fatigue, and myalgia were the most commonly reported AEs
- Per protocol dose reductions (12%), interruptions (12%) and treatment discontinuations (15%) were mainly due to hepatic AEs (ALT flares and/or hyperbilirubinemia)
- ALT flares and liver function abnormalities were generally correlated with HDV viral load decline
- No cases of clinical decompensation

10 CONCLUSIONS

- Lambda demonstrates comparable anti-HDV activity to historical PEG-Alfa at 24 weeks of treatment
- Lambda is well tolerated in the majority of patients
- The association of ALT flares with HDV viral load decline suggests a vigorous immune response to therapy rather than hepatotoxicity
- Interference with a bilirubin transporter molecule or immune related genes with viral interactions within the hepatocytes are the suspected causes of elevations of liver enzymes and hyperbilirubinemia
  - Additional case histories and further, more in-depth exploration in progress
- Lambda is a promising agent for mono or combination Rx development in the treatment of HDV

References

1 *Wobse et al, 2014 AASLD*
Wedemeyer et al, 2014 AASLD
2 *Chan et al, J Hepatology, 2016*