Tolerability and Safety of Peginterferon Lambda in Chronic HDV Infection

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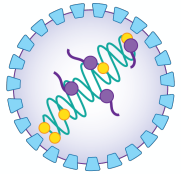
Disclosure

Honoraria for consulting or speaking and/or research grants:

Abbvie, Gilead, MSD, Eiger, HepQuant, CanFite, NeoPharm and ChemoMab

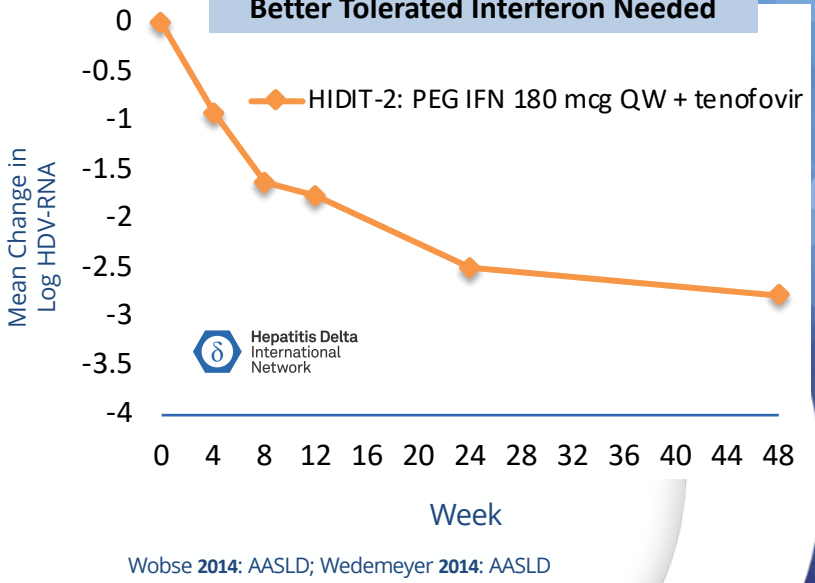
Hepatitis Delta Virus (HDV)



OVERVIEW

- Defective RNA virus
- Always associated with HBV infection
- Most severe form of chronic viral hepatitis
- Rapid progression to liver cirrhosis and cancer
- 15-20 M HDV infected patients worldwide
- No FDA approved Rx

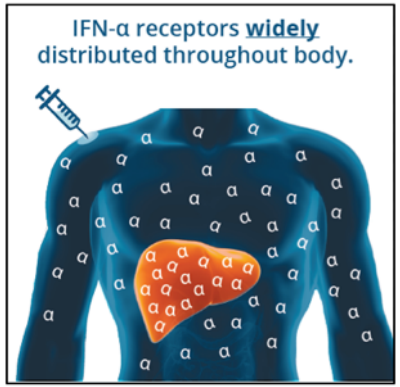
Severe Side-Effects with PEG IFN-alfa
Better Tolerated Interferon Needed

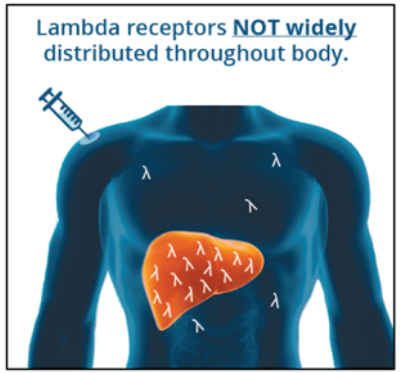


Wobse **2014**: AASLD; Wedemeyer **2014**: AASLD

Peginterferon Lambda

- A novel first in class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes and respiratory epithelium
  - 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)
- Comparable antiviral activity with less of the typical IFN alfa-related side effects*





* *Chan, HLY et al, J Hepatology 2016*

LIMT HDV “Mono”: Phase 2 Study

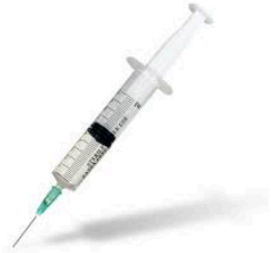
Objectives

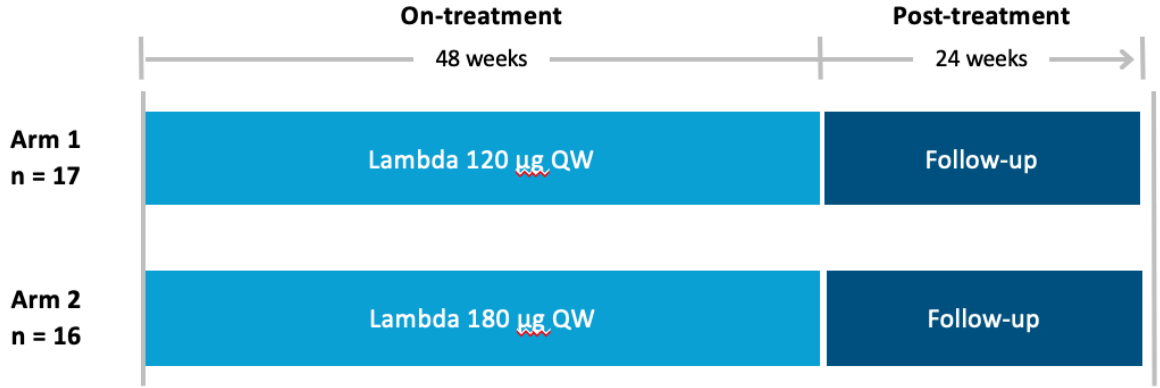
- Evaluate safety, tolerability and efficacy of Lambda monotherapy for 48 weeks
- Evaluate the proportion of patients with undetectable HDV RNA
  - 12 weeks after the end of treatment
  - 24 weeks after the end of treatment

4 Clinical Sites

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

LIMT HDV “Mono”: Phase 2 Study





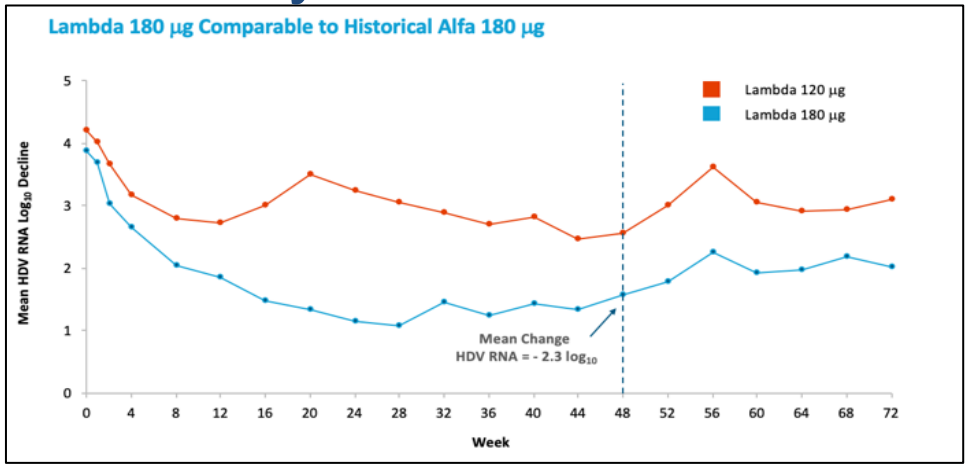
- Randomized, open-label study of Lambda 120 and 180 µg, weekly SC injections for 48 weeks in HDV patients
- Dose reductions permitted
- Major inclusion criteria: HDV RNA (+) by qPCR (Robogene® 2.0, BLQ 14 IU/mL), ULN<ALT<10×ULN, compensated liver disease
- Tenofovir or entecavir were started at baseline (BL)

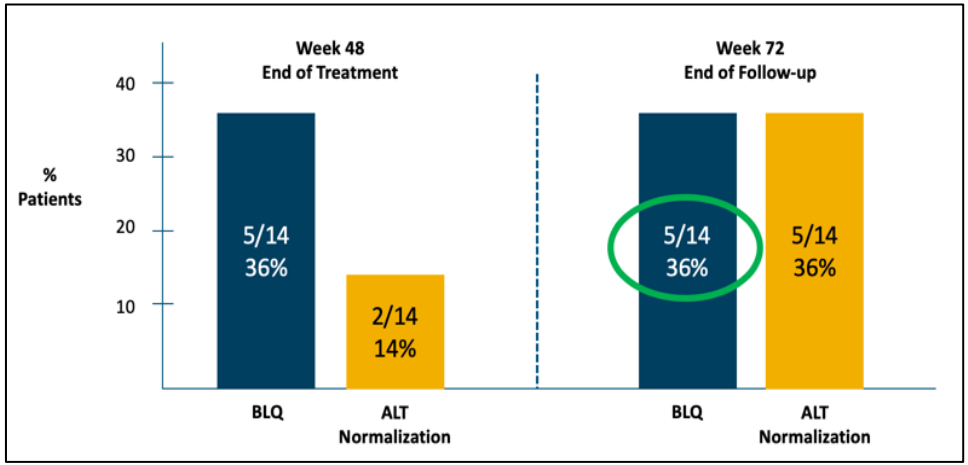
BLQ = below limit of quantification

LIMT Study: Baseline Characteristics

Median Characteristic Values	Values
N	33
Age, years (range)	36 (20, 63)
Male, n (%)	22 (66.7%)
Race, n (%) White Black Pacific Islander Other	 13 (39.4%) 1 (3.0%) 4 (12.1%) 15 (45.5%)
BMI, kg/m^2 (range)	24.7 (14.0, 37.1)
HDV-RNA, log_{10} IU/mL (range)	4.1 ± 1.4
ALT, U/mL (range)[1]	106 (35, 364)
Platelets, $x10^9/L$ (range)	170 (95, 281)
Albumin, g/dL (range)	4.4 (3.7, 5.2)
INR	1.2 (1.0, 1.5)
Bilirubin, mg/dL (range)[2]	0.5 (0.2, 1.2)
Cirrhotic (%)	9 (27%)
Prior Interferon Use (%)	21 (64%)

LIMT Study: Main Results





Etzion et al. EASL 2019

Treatment Emergent AEs of Special Interest

Classification	Number of Patients Experiencing Grade of AE (N=33)				
	Gr 1	Gr 2	Gr 3	Gr 4	Total
Constitutional	9	2	-	-	11 (33%)
Flu-like	14	7	1	-	22 (67%)
Neurological	13	6	2	-	21 (64%)
Musculoskeletal	14	5	1	-	20 (61%)
Psychiatric	-	-	-	-	0 (0%)
Hematologic	-	-	-	1	1 (3%)

- >90% of AEs are Grade 1 or 2
- No use of hematopoetic growth factors
- No incidences of depression/irritability

Serious & Significant AEs Leading to Dose Reduction/Interuption or Drug Discontinuation

- Total No: 17
- Hepatobiliary: 15 (88%)
  - Jaundice: 7 (41%)
  - ALT flare: 4 (23%)
- Drug discontimuation
  - Total No: 8
  - Pakistan cohort: 5 (62%)

LIRA-B Study:
AEs of Special Interest

Patients, n (%)	Lambda N=80 (%)	Alpha N=83 (%)
Constitutional	28 (35.0)	26 (31.3)
Neurologic	18 (22.5)	30 (36.1)
Flu-like	13 (16.3)	45 (54.2)
Musculoskeletal	5 (6.3)	23 (27.7)
Psychiatric	11 (13.8)	15 (18.1)
Hematologic	2 (2.5)	18 (22)

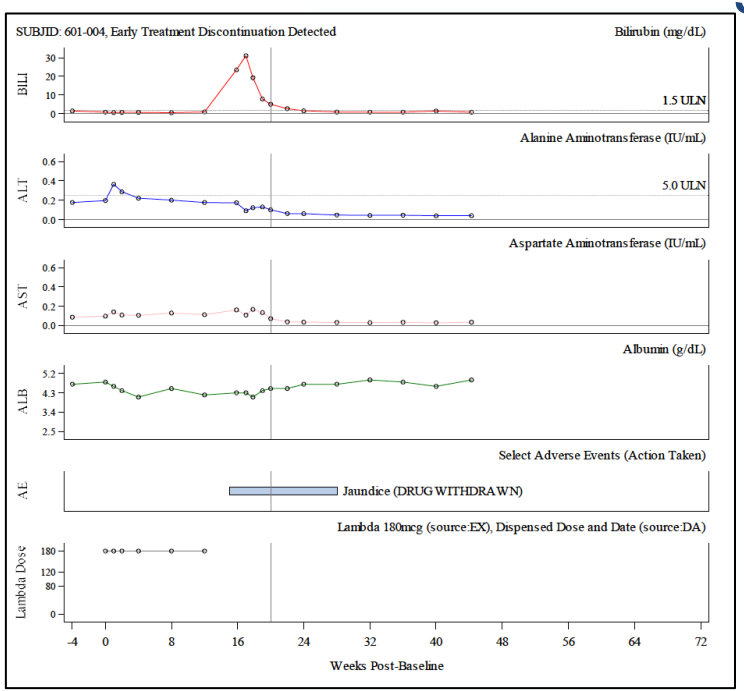
Adapted from Chan et al: J Hepatol. 2016

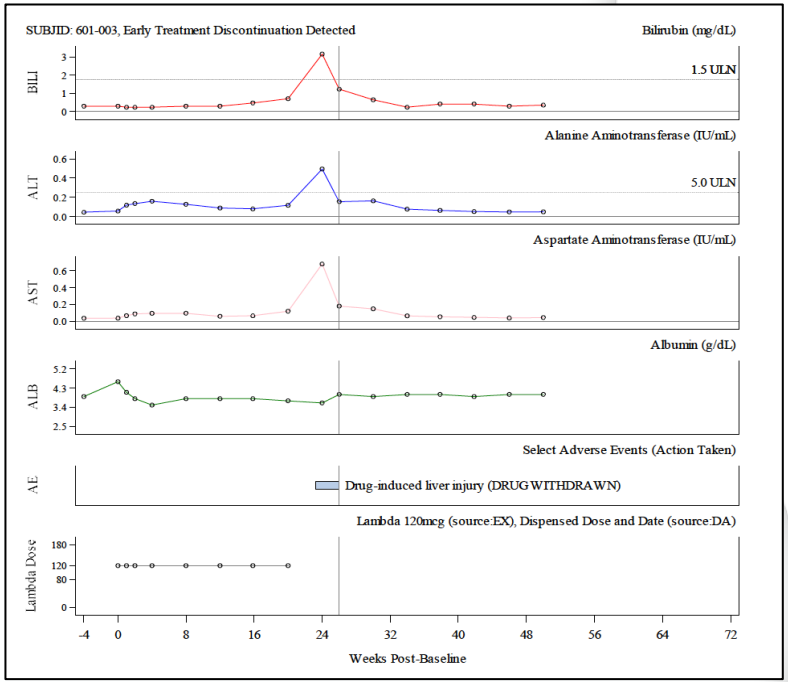
LIRA-B Study:
Grade III / IV Lab Abnormalities

Patients, n (%)	Lambda N=80	Alpha N=83
ALT > 5 X ULN	33 (41)	19 (23)
ALT flare	13 (16)	6 (7)
Bilirubin > 2.5 X ULN	3 (3.8)	0 (0)
Drug discontinuation	6 (7.5)	8 (9.6)

Adapted from Chan et al: J Hepatol. 2016

LIMT Study:
Clinical Course Following SAE

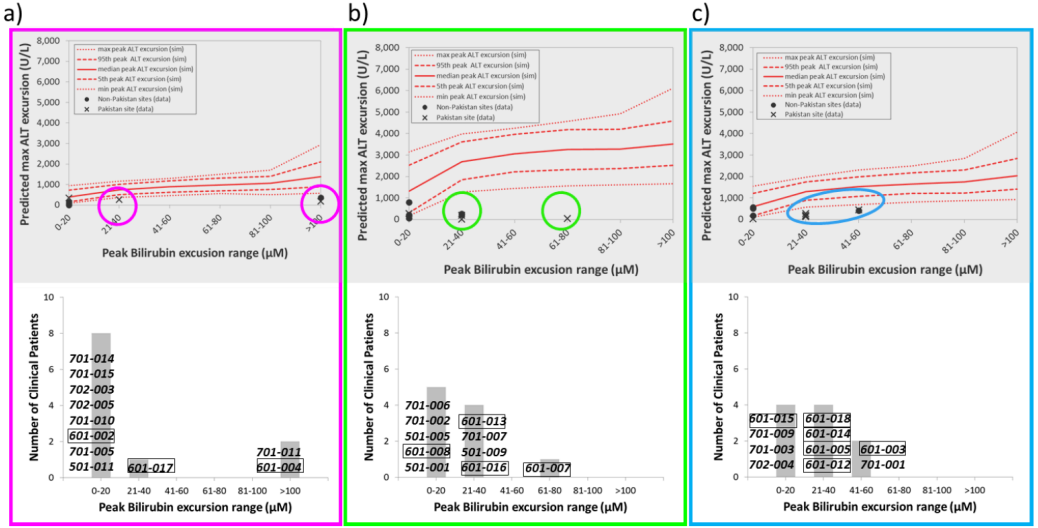




- Mostly asymptomatic
- No signs of decompensation
- Labs normalized within 4 weeks

Mechanism of ALT & Bilirubin Elevation DILIsym Analysis

- DILIsym- computational model for investigation of DILI mechanisms during the process of drug development
- Evaluation of ALT/AST and Tbili excrusions in Lambda treated patients
- Inferring magnitude of hepatocyte loss by approximating dynamic patterns observed with a reference population of patients with mild to



- Predicated hepatocyte loss <25%
- Bilirubin elevations are not consistent with significant liver necrosis
- Alteration transport/metabolism most plausible cause for Bili elevation

Summary

- Lambda shows a favorable tolerabilty profile in HDV infected patients
- Incidencies of Bilirubin and/or ALT elevations occured in a subset of patients mainly from the Pakistan cohort
- Clinical status was not compromised in affected patients and modeling suggest changes observed are not associated with substantial hepatocyte loss
- Liver enzymes and Bilirubin levels returned to baseline values following dose reduction/interruption or drug discontinuation
- Bilirubin elevations probably reflect changes in transport/metabolism rather than significant DILI

Conclusions

- Lambda shows promise as an efficacious drug for chronic HDV
- Patients treated with Lambda should be monitored closely for alterations in liver enzymes / bilirubin with treatment adjusted or stopped as needed