End of Study Results from LIMT HDV Study:
36% Durable Virologic Response at
24 Weeks Post-Treatment with
Pegylated Interferon Lambda Monotherapy in Patients with
Chronic HDV Infection

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HEPATITIS DELTA VIRUS (HDV)

OVERVIEW

- Most severe form of human viral hepatitis
- Most rapid progression to liver cirrhosis & cancer
- Always a co-infection with HBV
- 4-6% of HBV patients co-infected with HDV
- 15-20 M HDV infected patients worldwide
- No FDA approved Rx

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

HIDIT-2: PEG IFN 180 mcg QW + tenofovir

Mean Change in Log HDV-RNA

Week

Hepatitis Delta International Network

Wobse 2014: AASLD
Wedemeyer 2014: AASLD
**PEGINTERFERON LAMBDA**

A Better Tolerated Interferon

- A novel first-in-class Type III IFN
- Binds to a unique receptor versus Type I IFN
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells

Similar downstream signaling pathway as Type I IFN

- > 3,000 patients in 17 clinical trials (HCV / HBV)
- Less of the typical IFN alfa related side effects*

*Chan, HLY et al, J Hepatology 2016
Objectives

- Evaluate safety, tolerability and efficacy of Lambda monotherapy for 48 wks
  - Change in HDV RNA from BL to Week 48 and Week 72

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**

**Lambda Interferon MonoTherapy Study in HDV**

- 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 (BLQ 14 IU/mL)*, ULN<ALT<10×ULN, compensated liver disease
- Tenofovir or entecavir were started at baseline (BL)

*Robogene® 2.0, BLQ = below limit of quantification
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median Characteristic Values</th>
<th>Values</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>33</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>36 (20, 63)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>22 (66.7%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (39.4%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (45.5%)</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>24.7 (14.0, 37.1)</td>
</tr>
<tr>
<td>HDV-RNA, log₁₀ IU/mL (range)</td>
<td>4.1 ± 1.4</td>
</tr>
<tr>
<td>ALT, U/mL (range)¹</td>
<td>106 (35, 364)</td>
</tr>
<tr>
<td>Platelets, x10⁹/L (range)</td>
<td>170 (95, 281)</td>
</tr>
<tr>
<td>Albumin, g/dL (range)</td>
<td>4.4 (3.7, 5.2)</td>
</tr>
<tr>
<td>INR</td>
<td>1.2 (1.0, 1.5)</td>
</tr>
<tr>
<td>Bilirubin, mg/dL (range)²</td>
<td>0.5 (0.2, 1.2)</td>
</tr>
<tr>
<td>Cirrhotic (%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Prior Interferon Use (%)</td>
<td>21 (64%)</td>
</tr>
</tbody>
</table>

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
**HDV-RNA REDUCTION WITH LAMBDA**

Lambda 180 µg Comparable to Historical Alfa 180 µg

**Graph:**
- **Mean HDV RNA Log10 Decline**
- **Week**
- **Mean Change**
  - HDV RNA = - 2.3 log10
- **Lambda 120 µg**
- **Lambda 180 µg**
## Durable Virologic Response Demonstrated

For Low and High Baseline Viral Levels

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>48 Week On-Treatment</th>
<th>24 Week Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean Log&lt;sub&gt;10&lt;/sub&gt; Decline</td>
<td># BLQ</td>
</tr>
<tr>
<td>180 μg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>14</td>
<td>-2.3</td>
<td>5 / 14</td>
</tr>
<tr>
<td>High BL VL</td>
<td>8</td>
<td></td>
<td>3 / 8</td>
</tr>
<tr>
<td>Low BL VL</td>
<td>6</td>
<td></td>
<td>2 / 6</td>
</tr>
</tbody>
</table>

Low BL VL = low baseline viral loads of ≤ 4 log IU/mL
HIGH RESPONSE RATES WITH LAMBDA 180 MCG

Responder = 2 log decline or Below Limit of Quantification (BLQ) at End of Treatment

Week 48
End of Treatment

- **Lambda 180 µg**
  - BLQ: 36\% (5/14)
  - > 2 log₁₀ decline: 50\% (7/14)
- **Lambda 120 µg**
  - BLQ: 16\% (3/19)
  - > 2 log₁₀ decline: 21\% (4/19)
**DURABLE VIROLOGIC RESPONSE (DVR) DEMONSTRATED**

DVR = 36% BLQ at 24 Weeks Post-Treatment with Lambda 180 \( \mu g \)
ALT NORMALIZATION

ALT Continues to Normalize Post-Treatment

Week 48
End of Treatment

% Patients

Week 72
End of Follow-up

ALT Normalization

180 µg
5/14
36%

120 µg
2/14
14%

120 µg
2/19
11%

120 µg
5/19
26%
ALT NORMALIZATION & HDV RNA DECLINE
Endpoints for Liver Improvement and Virologic Response
## ADVERSE EVENTS: PREDOMINANTLY GRADE 1*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Adverse Event</th>
<th>Number of Patients Experiencing Grade of AE (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gr 1</td>
</tr>
<tr>
<td>Constitutional</td>
<td>fatigue, asthenia</td>
<td>10</td>
</tr>
<tr>
<td>Flu-like</td>
<td>pyrexia, chills, chest pain, flu-like</td>
<td>21</td>
</tr>
<tr>
<td>Neurological</td>
<td>dizziness, headache</td>
<td>17</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>arthralgia, myalgia, back pain, musculoskeletal</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>pain</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>depression, irritability, insomnia</td>
<td>1</td>
</tr>
<tr>
<td>Hematological</td>
<td>neutrophil count decreased</td>
<td>-</td>
</tr>
<tr>
<td>Lab Abnormalities</td>
<td>bilirubin / ALT / AST / GGT increase</td>
<td>2</td>
</tr>
</tbody>
</table>

- Milder flu-like and psychiatric symptoms with Lambda
- No thrombocytopenia events, no use of hematopoietic growth factors
- Elevated bilirubin and ALT levels normalized upon dose reduction or treatment discontinuation

* >1300 Weeks of Treatment  
** non-serious
PAKISTAN COHORT

Higher Instances of Hyperbilirubinemia

- 15 of 33 (45%) patients randomized to Pakistan

- Hyperbilirubinemia in 4/15 (27%) vs 2/18 (11%) of non-Pakistani patients

- Jaundice observed in 3/15 (20%) vs 0/18 (0%) of non-Pakistani patients

- Patients with bilirubin elevations had no symptoms of decompensation
  - Bilirubin levels were responsive to dose reduction/interruption

- Incidence/severity in non-Pakistani cohort consistent w/ prior Lambda and Alfa data in HBV\(^1\)

- Transporter-based mechanism for bilirubin elevations\(^2\)

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\(^1\) Chan et al J. Hepatology 2016; Pegasys\(^\circ\) package insert; \(^2\) Determined by DILISYM\(^\circ\) modeling of ALT and bilirubin dynamics
LIMT STUDY OBSERVATIONS

- 33 patients were randomized to Lambda 180 μg (N=14) or 120 μg (N=19)

- ITT rates of durable virologic response (DVR=BLQ at 24 wks post-tx) for Lambda 180 μg = 5 of 14 (36%)

- Lambda was well tolerated overall

- Increased incidences of clinical jaundice and bilirubin elevations were observed in the Pakistani cohort
  - Led to lower than expected rate of study completion (9 of 15, 60%) for Pakistan site
  - Israel and New Zealand sites had completion rates (15 of 18, 83%) comparable to prior Alfa studies

- None of the patients with elevations in bilirubin showed symptoms of decompensation
  - All responded favorably to dose reduction or dose discontinuation

ITT = intent to treat
**LIMT STUDY CONCLUSIONS**

- Durable BLQ virologic responses have been observed 24 weeks post-treatment

- ITT rates of DVR of Lambda (36%) compares favorably to historic rates for Alfa 180 µg (28%)*

- Common on-treatment AEs included mild to moderate flu-like symptoms and elevated transaminase levels

- Patients previously treated with Alfa noted significantly less side effects on Lambda

- No patients requested discontinuation of treatment

- Lambda is a promising agent for mono and/or combination drug development in the treatment of HDV

- Phase 2 **LIFT** combination study with Lambda + Lonafarnib is on-going at NIH

* Wedemeyer et al; NEJM, 2011
DVR = BLQ at 24 wks post-treatment
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