A Phase 2 Dose-Optimization Study of Lonafarnib with Ritonavir for the Treatment of Chronic Delta Hepatitis —End of Treatment Results from the LOWR HDV-2 Study

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Disclosures

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- Advisory Boards: Merck, Janssen, AbbVie and Gilead
- Speakers Bureau: Roche, AbbVie, Eiger BioPharmaceuticals and Gilead
- Has received research grants from Roche, BMS Pharma and Eiger

Jeffrey Glenn
- Board, Founder: Eiger, Riboscience
- Consulting: Gilead, Janssen, Sundise, Genentech, Merck, Roche, Romark, StemCells
- Equity interest in Eiger

All remaining authors have no financial relationships to disclose.
Hepatitis Delta Virus
Leads to the Most Severe Form of Viral Hepatitis

- **HDV leads to the most severe form of viral hepatitis**
  - More rapid progression to liver cirrhosis
  - 5-7x more likely to develop cirrhosis and HCC vs HBV

- **HDV is always associated with HBV infection**
  - HDV steals HBsAg from HBV for envelopment

- **Final step in replication involves prenylation**
  - HDV hijacks prenylation, a host process

- **No FDA approved Rx for HDV**
  - PEG IFN-α demonstrates modest benefit

- **HDV worldwide prevalence is 15 - 20 million**
  - Approximately 4-6% of HBV worldwide population is infected with HDV
  - Orphan status in US and EU
**HDV Life Cycle**

- **Uncoating of Virus**
- **Transport to Nucleus**
- **Replication**
- **Assembly**
- **Release of Progeny**

- HDV genome
- Small delta antigen
- Large delta antigen
- Prenylated LHDAg
- Prenyl moiety
- HBsAg

- **HDV genome**
- **small HDAg**
- **large HDAg**
- **prenylated LHDAg**
- **prenyl moiety**
- **HBsAg**
**Sarasar® (lonafarnib) for HDV**
*Well-Characterized Clinical Stage Lead Compound*

- Small molecule, oral, prenylation inhibitor
- Well-characterized through Phase 3
  - >2,000 patients dosed in oncology program by Merck (Schering)
  - Dose limiting toxicity is GI (class effect)
- Prenylation is a host target; potential high barrier to resistance
- Over 120 HDV patients dosed across international sites
  - NIH Phase 2 study results published in *Lancet Infectious Diseases* 2015*
- Orphan Designation in US & EU, Fast Track in US

LOWR HDV - 2, - 3, - 4
Week 48 Results Presented at EASL 2017

LOWR HDV – 2
“Dose-Ranging”
N = 58

LOWR HDV – 3
“QD Dose”
N = 21

LOWR HDV – 4
“Dose-Escalation”
N = 15

LOWR HDV – 2
• Identify LNF-RTV combination +/- PEG IFN

LOWR HDV – 3*
• Once-daily dosing

LOWR HDV – 4**
• Is rapid dose-escalation possible and / or required?

* Koh et al., EASL 2017 Abstract #LBP-519, ** Wedemeyer et al., EASL 2017 Abstract #PS-039
Purpose

- To identify combination regimens of LNF and RTV ± PEG IFN-α which demonstrate efficacy and tolerability for longer term dosing to enable HDV-RNA clearance.

Patients and Methods

- Treatment duration 12 or 24 or 48 weeks
- 72 hour PK and PD evaluation on day 1 and day 28
- Testing frequency: days 1, 2, 3, 7, 14, 28 and then 4W
  - Biochemical parameters, HBV DNA
  - HDV-RNA (by in-house qPCR with LOQ ~ 3 log copies/mL)

LOQ = limit of quantitation
LOWR HDV – 2: “Dose Finding” Study
Tolerability, Longer Dosing, and Triple Combination

High Dose

Weeks 1-12

LNF $\geq 75$ mg BID + RTV

N=19

Weeks 13-24-48

Low Dose: All-Oral

LNF 50 mg BID or LNF 25 mg BID + RTV 100 mg BID

N=20

Low Dose: Triple Combination

LNF 50 mg BID or LNF 25 mg BID + RTV 100 mg BID + PEG IFN $\alpha$ 180 mcg QW

N=19

N=58
## LOWR HDV – 2: “Dose Finding” Study

Low Doses Tested for Longer Durations

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration (Weeks)</th>
<th># Patients</th>
<th># Discontinuations Due to AE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L100B + R100Q</strong></td>
<td>12</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>L150Q + R100Q</strong></td>
<td>12</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>L100B + R50B</strong></td>
<td>12</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>L100Q + R100Q</strong></td>
<td>12</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>L75B + R100B</strong> (+ P180QW on Wk 12)</td>
<td>24</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>L50B + R100B</strong> (+ P180QW on Wk 12)</td>
<td>24</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>L50B + R100B</strong></td>
<td>24</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>L25B + R100B</strong></td>
<td>24</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>L50B + R100B + P180QW</strong></td>
<td>24</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>L25B + R100B + P180QW</strong></td>
<td>24</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>58</td>
<td>6</td>
</tr>
</tbody>
</table>

$L=$LNF in mg, $R=$RTV in mg, $P=$PEG IFN-α in mcg, $B=$BID, $Q=$QD
### Baseline Characteristics

**LOWR HDV – 2: Low Dose Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>27*</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>50 (24 - 59)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>12 (44%)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>27 (100%)</td>
</tr>
<tr>
<td><strong>Median BMI, kg/m(^2) (range)</strong></td>
<td>24.5 (18.5 – 33.9)</td>
</tr>
<tr>
<td><strong>Median HDV-RNA, log(_{10}) copies/mL (range)</strong></td>
<td>5.36 (3.30 – 6.94)</td>
</tr>
<tr>
<td><strong>Median ALT, U/mL (range)</strong></td>
<td>64 (24 - 229)</td>
</tr>
<tr>
<td><strong>Prior interferon treatment, n (%)</strong></td>
<td>12 (44%)</td>
</tr>
</tbody>
</table>

* Excludes 7 patients < LOQ at baseline
# LOWR HDV – 2: Efficacy

As-Treated Analysis: Patients Dosed for 24 Weeks

<table>
<thead>
<tr>
<th></th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>All-Oral Rx</strong></td>
</tr>
<tr>
<td>LNF 25 mg BID + RTV</td>
<td>N = 6</td>
</tr>
<tr>
<td>LNF 50 mg BID + RTV</td>
<td>N = 8</td>
</tr>
<tr>
<td>LNF 25 mg BID + RTV + PEG</td>
<td>N = 5</td>
</tr>
<tr>
<td>LNF 50 mg BID + RTV + PEG</td>
<td>N = 4</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
</tr>
<tr>
<td>HDV-RNA &lt; LOQ</td>
<td>3 / 6</td>
</tr>
<tr>
<td>HDV-RNA PCR negative</td>
<td>0 / 6</td>
</tr>
<tr>
<td>&gt; 2 log decline*</td>
<td>3 / 5</td>
</tr>
</tbody>
</table>

**24 Week Dosing**

- **All-oral LNF 25 and 50 mg BID + RTV suppress HDV-RNA < LOQ in 36% of patients**
- **Addition of PEG IFN to LNF 25 mg BID + RTV enhances antiviral activity**

* Patients with high baseline viral load (HDV RNA > 5 log copies/mL)
### LNF 25 mg BID + RTV + PEG

2 Patients HDV-RNA negative at EOT (Week 24) and Week 48

<table>
<thead>
<tr>
<th></th>
<th># of Patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Oral Rx</td>
<td>Triple Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LNF 25 mg BID + RTV</td>
<td>LNF 50 mg BID + RTV</td>
<td>LNF 25 mg BID + RTV + PEG</td>
<td>LNF 50 mg BID + RTV + PEG</td>
</tr>
<tr>
<td>Week 24</td>
<td>N = 6</td>
<td>N = 8</td>
<td>N = 5</td>
<td>N = 4</td>
</tr>
<tr>
<td>HDV-RNA &lt; LOQ</td>
<td>3 / 6</td>
<td>2 / 8</td>
<td>4 / 5</td>
<td>3 / 4</td>
</tr>
<tr>
<td>HDV-RNA PCR negative</td>
<td>0 / 6</td>
<td>1 / 8</td>
<td>3 / 5</td>
<td>0 / 4</td>
</tr>
<tr>
<td>&gt; 2 log decline*</td>
<td>3 / 5</td>
<td>1 / 3</td>
<td>3 / 4</td>
<td>3 / 3</td>
</tr>
</tbody>
</table>

- 3 of 5 patients (60%) PCR-negative at Week 24
  - 2 had low viremia off-therapy, PCR-negative at 24 weeks post-treatment
  - 1 continued treatment for another 24 weeks

*Patients with high baseline viral load (HDV RNA > 5 log copies/mL)*
# LOWR HDV – 2: Efficacy
## As-Treated Analysis: Patients Dosed for 48 Weeks

### # of Patients

<table>
<thead>
<tr>
<th></th>
<th>All-Oral Rx</th>
<th>Triple Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LNF 25 mg BID + RTV</td>
<td>LNF 50 mg BID + RTV</td>
</tr>
<tr>
<td>Week 24</td>
<td>N = 6</td>
<td>N = 8</td>
</tr>
<tr>
<td>HDV-RNA &lt; LOQ</td>
<td>3 / 6</td>
<td>2 / 8</td>
</tr>
<tr>
<td>HDV-RNA PCR negative</td>
<td>0 / 6</td>
<td>1 / 8</td>
</tr>
<tr>
<td>&gt; 2 log decline*</td>
<td>3 / 5</td>
<td>1 / 3</td>
</tr>
<tr>
<td>Week 48</td>
<td>N = 5</td>
<td>N = 2</td>
</tr>
<tr>
<td>HDV-RNA &lt; LOQ</td>
<td>2 / 5</td>
<td>1 / 2*</td>
</tr>
<tr>
<td>HDV-RNA PCR negative</td>
<td>0 / 5</td>
<td>0 / 2*</td>
</tr>
<tr>
<td>&gt; 2 log decline*</td>
<td>1 / 4</td>
<td>0 / 0</td>
</tr>
</tbody>
</table>

### 48 Week Dosing
- **All-oral LNF:** 3 of 7 patients (43%) < LOQ
- **Triple LNF 25 mg BID + RTV + PEG:** 2 of 3 patients (67%) PCR-negative

* Patients with high baseline viral load (HDV RNA > 5 log copies/mL); * Week 40-44 data
60-78% of Patients Normalized ALT at Wk 24*

Addition of PEG Improves ALT Normalization

* LNF 25 and 50 mg BID regimens with elevated ALT at baseline
All-Oral Rx = LNF 25/50 mg BID + RTV 100 mg BID; Triple Rx = LNF 25/50 mg BID + RTV 100 mg BID + PEG IFN 180 mcg QW
### Adverse Events: Low Dose LNF

**LNF 25 / 50 mg Regimens Demonstrate Tolerability**

<table>
<thead>
<tr>
<th>AE Grade</th>
<th>All-Oral Rx</th>
<th>Triple Rx</th>
</tr>
</thead>
</table>
|          | LNF 25 mg BID + RTV  
* N = 6 | LNF 50 mg BID + RTV  
* N = 14 | LNF 25 mg BID + RTV + PEG  
* N = 9 | LNF 50 mg BID + RTV + PEG  
* N = 10 |
| Grade 1  | 3           | 8         | 4          | 5          |
| Grade 2  | 1           | 3         | 2          | 4          |
| Grade 3  | 2           | 2         | 0          | 1          |
| SAE³     | 1           | 2         | 1          | 1          |

- **AEs predominantly mild / moderate for LNF 25 / 50 mg regimens**
- **Generally tolerable through Week 48**

*Highest grade GI AE reported*

1. Most common and severe reported AEs: nausea, diarrhea, fatigue, weight loss, anorexia, vomiting
2. Includes cohort: LNF 50 mg BID + RTV for first 12 weeks + PEG for second 12 weeks
3. All reported to be “unlikely related to LNF”
LOWR HDV – 2
Conclusions

• All-oral LNF 25 or 50 mg BID + RTV suppresses HDV-RNA < LOQ
  - 5 of 14 (36%) patients < LOQ at Week 24
  - 1 patient PCR-negative at Week 24

• Addition of PEG IFN to LNF 25 mg BID + RTV results in highest response
  - 4 of 5 (80%) patients < LOQ at Week 24
  - 3 of 5 (60%) patients PCR-negative at Week 24
    ▪ 2 patients PCR-negative at 24 weeks post-treatment

• 60-78% of patients normalized ALT at Week 24

• > 2 log decline AND normalized ALT warrants evaluation for clinical benefit

• AEs predominantly mild / moderate for LNF 25 / 50 mg regimens