A Phase 2 Dose-Escalation Study of Lonafarnib Plus Ritonavir in Patients with Chronic Hepatitis D: Final Results from the Lonafarnib With Ritonavir in HDV - 4 (LOWR HDV - 4) Study

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Disclosures

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Hepatitis D (Delta) - Virus

- Defective virus that needs HBsAg for its propagation
- 10-20 million individuals are anti-HDV positive
- Causes the most severe form of chronic viral hepatitis

More rapid progression to liver cirrhosis and liver cancer; 5-7x more likely to develop cirrhosis and HCC vs HBV

48 wks of PEG IFN-α leads to 25-30% undetectable HDV-RNA

Wedemeyer, Yurdaydin et al., NEJM 2011; 364: 322-31

Late relapses occur in 56% of patients with initial response

Heidrich et al., Hepatology 2014; 60:87-97

HDV-RNA suppression is associated with improved long-term clinical outcome

Wranke et al., Hepatology 2016 epub, Oct 22

Final step in HDV replication involves prenylation (i.e. farnesylation):
• Farnesyl transferase is a host enzyme which can be targeted by drugs
• Lonafarnib for 28 days induced a dose-dependent HDV-RNA decline

Koh et al., Lancet Infect. Dis. 2015; 15: 1167-74
Lonafarnib for HDV

- Small molecule, oral, prenylation inhibitor

- Well-characterized through Phase 3
  - >2,000 patients dosed in oncology program by Merck (Schering-Plough)
    (RAS and HDV large antigen share the same farnesyl modification)
  - Dose limiting GI toxicity (class effect)

- Over 120 HDV patients dosed across international sites
LOWR HDV Program
Identifying Dose and Regimen for Registration Study

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

LOWR HDV – 3
“QD” Study
N = 21

LOWR HDV – 4
“Dose-Escalation” Study
N = 15

LOWR HDV – 2*
• LNF-RTV +/- PEG IFN
  • Yurdaydin et al. EASL 2017 Abstract #GS-008

LOWR HDV – 3**
• Koh et al., EASL 2017 Abstract #LBP-519
Primary Objectives
- Dose-escalation / maintenance up to LNF 100 mg BID + RTV for 24 weeks
- Safety and tolerability of LNF + RTV dose-escalation for 24 weeks
- HDV-RNA decline over 24 weeks

Secondary Objectives
- Pharmacokinetics
- ALT normalization
- Change in HBV-DNA levels
- Post-treatment HDV-RNA levels

HDV-RNA quantified by Robogene 2.0: LLOD = 14 IU/mL
LOWR HDV – 4: Dose-Escalation Study

Study Completed: 24 Weeks Rx + 24 Weeks Follow-Up

LOWR-4: Lonafarnib for Hepatitis Delta

Wedemeyer et al. 04--2017
### Baseline Characteristics

**LOWR HDV - 4**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>40 (25 - 66)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>11 (73.3%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>26.1 (20.8 - 34.3)</td>
</tr>
<tr>
<td>HDV-RNA, log₁₀ IU/mL (range)</td>
<td>4.58 (2.76 - 6.28)</td>
</tr>
<tr>
<td>ALT, U/mL (range)</td>
<td>118 (54 - 362)</td>
</tr>
<tr>
<td>Fibroscan, kPa (range)</td>
<td>14.4 (3.6 - 35.3)</td>
</tr>
<tr>
<td>Prior interferon treatment, n (%)</td>
<td>10 (73%)</td>
</tr>
<tr>
<td>NUC treatment from baseline, n (%)</td>
<td>12 (80%)</td>
</tr>
</tbody>
</table>
LOWR HDV – 4: Dose-Escalation Study
Lonafarnib Doses

- N = 15
  - 50 mg BID
  - N = 1
    - 75 mg BID
    - N = 13
      - Dose reduced
      - N = 10
        - 100 mg BID
        - N = 0
          - 75 mg BID
          - N = 3
            - Dose reduced
            - N = 5
              - Dose reduced
              - N = 5
                - 100 mg BID

Ritonavir adjustments not shown
LOWR HDV – 4: Dose-Escalation Study

Patient Disposition

≥ 4 Weeks
≥ 2 Weeks
18 Weeks

N = 15
50 mg BID

N = 1
50 mg BID

Dose reduced

N = 13
75 mg BID

N = 0
75 mg BID

Dose reduced

N = 10
100 mg BID

N = 5
100 mg BID

Dose reduced

N = 5
75 mg BID

Dose reduced

N = 1
100 mg QD discontinued

N = 1
50 mg QD discontinued

Ritonavir adjustments not shown
5 Patients Maintained on LNF 100 mg BID
Through Week 24

≥ 4 Weeks  ≥ 2 Weeks  18 Weeks

N = 15
50 mg BID

N = 13
75 mg BID

N = 1
50 mg BID

N = 1
Dose reduced

N = 10
100 mg BID

N = 0
75 mg BID

N = 3
Dose reduced

N = 5
100 mg BID

N = 5
Dose reduced

5/15 patients: full dose

Ritonavir adjustments not shown
### Safety

**GI Adverse Events and Weight Through Week 48**

<table>
<thead>
<tr>
<th>AE Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
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<td>7</td>
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#### Baseline vs Week 24

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<td>Mean Wt change from BL</td>
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<td>-5.6 kg</td>
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- 8 GI/weight loss AEs present at Week 48 (end of follow-up)
- 1 SAE: traumatic broken jaw during follow-up (unrelated to treatment)
## Safety

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<td>Mean Wt change from BL</td>
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<td>-2.2 kg</td>
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- 8 GI/weight loss AEs present at Week 48 (end of follow-up)
- 1 SAE: traumatic broken jaw during follow-up (unrelated to treatment)
HDV-RNA Drop From Baseline
13 Patients Across 24 Weeks

Mean decline after 24 weeks (ITT):
-1.7 log IU/mL (SD ± 1.5 )

% with > 1 log decline: 9/15 (60%)
% with > 2 log decline: 4/15 (27%)

Pt 14: HDV-RNA < LLOQ @ Week 24
Pt 3: HDV-RNA undetectable @ Week 24
HDV-RNA Drop From Baseline

13 Patients Across 48 Weeks

> 2 log decline @ 48 Wk: 3/15 (20%)

Pt 14: HDV-RNA < LLOQ

Log HDV-RNA IU / mL

Week

EOT

EOFU

LLOD

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LOWR-4: Lonafarnib for Hepatitis Delta
Responders
Maintained LNF 100 mg BID Through Wk 24

Patient 3
- 75 mg BID
- 100 mg BID

Patient 14
- 75 mg BID
- 100 mg BID

- HDV-RNA PCR negative @ Week 24
- HDV-RNA <LLOQ @ Week 16-24
- HDV-RNA <LLOQ @ Week 48
Post-treatment Responder & Relapser

Patient 5

- 75 mg BID
- 100 mg BID

Patient 2

- 75 mg QD
- 75 mg BID

- VL continues to decline post-treatment
- ALT flare = 938 U/L @ Week 32

- 4-log decline @ Week 24
Non - Responders

Patient 18

75 mg BID
100 mg BID
50 mg BID

Log Viral Load IU/mL

Week
EOT
EOFU

ALT (U/L)

Log HDV-RNA IU/mL

Patient 16

75 mg BID
100 mg BID

Log Viral Load IU/mL

Week
EOT
EOFU

ALT (U/L)

Log HDV-RNA IU/mL

• HDV RNA < 1 log decline at Week 24

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LOWR-4: Lonafarnib for Hepatitis Delta
ALT Normalization

53% Patients Normalized ALT at End of Treatment
All Patients with Elevated ALT at End of Follow-Up

* ITT is shown including 2 early terminations
LOWR HDV – 4: Summary

At Week 24 – End of Treatment:
- 5/15 (33%) reached and maintained LNF 100 mg BID + RTV through EOT
  - 1/5 HDV-RNA undetectable; 1/5 dropped < 14 IU/mL (LLOQ)
- 53% patients normalized ALT

At Week 48 – End of Follow-up:
- 1/15 (7%) HDV RNA < 14 IU/mL (LLOQ)
- 3/15 (20%) dropped > 2 logs from baseline

Gastrointestinal AEs
- mostly grade 1-2
- 8/15 (53%) required dose reduction and 2/15 (13%) were discontinued

Inter-patient variability in efficacy and tolerability of LNF

Ongoing analysis:
- Role of host polymorphisms to explain interindividual variability in viral responses
- Role of host immune responses against HDV explaining long-term control
Conclusions

• This study confirmed an antiviral efficacy of lonafarnib over a period of 24 weeks

• Off-treatment HDV RNA control is possible in a proportion of patients

• Longer therapies and combination therapies need to be explored
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