RO7020531, a novel prodrug of a toll-like receptor 7 agonist, demonstrated desirable pharmacodynamics responses in both AAV-HBV mice and healthy volunteers

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Roche Approach Toward Combination Therapy for HBV Cure

Functional impairment of anti-HBV immune responses is a key feature of chronic HBV infection. Development of a finite HBV cure will likely require combinations of novel compounds which inhibit HBV replication, reduce antigen production and enhance HBV-specific immune responses.

CpAM: core protein allosteric modulator; LNA: locked nucleic acid; SoC: standard of care; IFN: interferon; TLR: toll-like receptor
Roche TLR7 agonist is positioned to be differentiated as an oral double prodrug selectively converted in the liver

- TLR7 agonist induces broad immuno-modulatory effects including:
  - Activation of IRF7, NFκB, and AP-1 transcription factors
  - Differentiation of plasmacytoid dendritic cells (pDCs), and upregulation of co-stimulatory molecules and secretion of type 1-IFN and other cytokines/chemokines leading to activation of T-cells and NK cells
  - Differentiation of B-cells to antibody-producing plasma cells
- RO7020531 is an orally available double pro-drug of a TLR7 agonist which also activates TLR8 with lower potency
- It was safe and well tolerated in healthy volunteers with a favorable PK profile in single and multiple QOD doses up to 170 mg

Dai, L. et al. [poster]. EASL 2018; SAT-345; Gane, E. et al. [poster]. EASL 2018; FRI-337
In the AAV-HBV mouse model, oral combination treatment with TLR7 agonist RO7020531 and CpAM RO7049389 leads to sustained viral load suppression and HBsAg loss.

- The combination of RO7049389 and RO7020531 reduced HBsAg level to below LLOQ at the end of treatment in 5 of 7 animals, which sustained during 6-week off-treatment follow-up.

Results are presented as mean±SEM (n = 7). LLOQ = lower limit of quantification; QD = once a day; QOD = every other day.

Dai et al EASL 2018; SHC 2018, GHS 2018
RO7020531 increases the number of germinal center B cells and HBsAg-specific B and T cells in the spleen of AAV-HBV infected mice

- HBsAg-specific B cells were captured and measured by ELISPOT with HBsAg-coated plate.
- HBsAg-specific T cells were measured by IFN-γ ELISPOT in the presence of HBsAg peptides.
The anti-HBV activity of RO7020531 in AAV-HBV infected mice relies on functional adaptive immune response (B- and T- cells)

• Note: no change on HBeAg level was observed.
• Increasing dose levels of RO7020531 in SCID mice up to 300 mg/kg did not demonstrate anti-HBV activity.
• Plasma exposure of TLR7 agonist and innate immune responses (mRNA upregulation of interferon induced genes) in both SCID and C57B/Bl6 mice were comparable.
The PD response of TLR7 signalling is observed in a dose-dependent manner in RO7020531-treated AAV-HBV mice.

*m* Mouse blood samples were collected at 6 hours post dose on day 28 for mRNA and cytokine tests.
TLR7 agonist RO7020531 Phase 1 umbrella study (NP39305)

- First-in-human study for RO7020531
- 110 healthy volunteers dosed in Part 1
- HBV patient part initiated in 2018 (cohort 1 to 3 in Nuc-suppressed patients completed)

**Part 1: Completed**

- SAD in HV: 1 single dose
- MAD in HV: 2 weeks of QOD dosing

**Part 2: cohort 1 to 3 completed**

- Safety / PD Study in HBV Patients: 6 Weeks QOD treatment, 6 Weeks follow-up
- Cohort 1: 3 mg, 10 mg, 20 mg, 40 mg, 60 mg, 100 mg, 140 mg, 170 mg QOD
- Cohort 2: 170 mg QOD Rx naive
- Cohort 3: 170 mg QOD
- Cohort 4: 150 mg QOD Rx naive

Gane, E. et al. [poster]. EASL 2018; FRI-337
Gane, E. et al. SHC, 2018
Jin, Y. et al. APASL STC, 2019
RO7020531 has a favorable pharmacokinetics profile

- **Dose proportional exposure** across the full RO7020531 dose range (3 mg–170 mg) in SAD and MAD

- The active TLR7 agonist appears rapidly in plasma with a median $T_{\text{max}}$ of ~0.5 hrs, is cleared within 12 hours post dose (mean half life ~ 3.0 hr)

- **Stable RO7011785 exposure over a two week dosing** with no drug accumulation

- Following multiple QOD RO7020531 doses, there was **no evidence for RO7011785 accumulation**, and PK parameters on Day 1 and Day 13 in the MAD were comparable

**Concentration-time profiles for RO7011785 (active agonist) following multiple QOD RO7020531 doses**

Day 1

Day 13

Gane, E. et al. SHC, 2018; Jin, Y. et al. APASL STC, 2019
Pharmacodynamic activity first demonstrated at 100 mg (SAD)

- PD Evaluations: TLR activation markers in serum (IFN-α, IL-6, TNF-α, IL-10, IL-12p40, IP-10 and neopterin) and expression of ISG15, OAS-1, MX1 and TLR7 mRNAs in whole blood

- Following a single 100 mg RO7020531 dose, 3/8 subjects exhibited increases in IFN-α indicative of TLR7 activation (Panel A)

- These changes in IFN-α were accompanied by increases above baseline for other markers of TLR7 activation including ISG-15 and OAS-1 shown as an example for Subject 1 (Panel B) following the expected temporal pattern after the appearance of plasma RO7011785

Gane, E. et al. SHC, 2018; Jin, Y. et al. APASL STC, 2019
Higher RO7020531 doses yields more ‘responders’ and with a greater amplitude of response (SAD cohorts)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Fraction responding</th>
<th>Geometric mean fold change (range)</th>
<th>Fraction responding</th>
<th>Geometric mean fold change (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISG15</td>
<td></td>
<td>OAS1</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0/16</td>
<td>-</td>
<td>0/16</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1/8</td>
<td>2.4 (2.4–2.4)</td>
<td>0/8</td>
<td>-</td>
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<tr>
<td>10</td>
<td>0/8</td>
<td>-</td>
<td>0/8</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>1/8</td>
<td>2.6 (2.6–2.6)</td>
<td>0/8</td>
<td>-</td>
</tr>
<tr>
<td>40</td>
<td>1/8</td>
<td>2.9 (2.9–2.9)</td>
<td>0/8</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>1/8</td>
<td>2.6 (2.6–2.6)</td>
<td>2/8</td>
<td>2.4 (2.0–2.9)</td>
</tr>
<tr>
<td>100</td>
<td>6/8</td>
<td>5.9 (2.3–29.3)</td>
<td>5/8</td>
<td>3.8 (1.9–6.9)</td>
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<tr>
<td>140</td>
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<td>11.6 (2.3–48.0)</td>
<td>8/8</td>
<td>5.5 (2.2–18.1)</td>
</tr>
<tr>
<td>170</td>
<td>8/8</td>
<td>11.2 (2.5–132.2)</td>
<td>8/8</td>
<td>5.5 (2.0–19.0)</td>
</tr>
</tbody>
</table>

With increasing single dose, the fraction of subjects exhibiting TLR7 PD activity and the magnitude of response increased with a plateau of geometric mean response magnitude at 170 mg.

Gane, E. et al. SHC, 2018; Jin, Y. et al. APASL STC, 2019
PD activity maintained across multiple biomarkers with QOD dosing of RO7020531

In the MAD cohorts, biomarker response was maintained over the 2 week QOD dosing

**INF-α**

![INF-α graph]

**ISG15 mRNA**

![ISG15 mRNA graph]

Jin, Y. et al. APASL STC, 2019
Summary

• RO7020531 is a novel double pro-drug of a TLR7 agonist.

• In the AAV-HBV mouse model, RO7020531 induced both innate PD responses and adaptive immune responses which are important for therapeutic effects. The oral combination of the CpAM and TLR7 agonist demonstrated robust suppression of both HBsAg and HBV DNA levels and with the additional emergence of anti-HBs antibodies in several animals.

• RO7020531 appears to be safe and tolerable with a predictable PK profile for the active TLR7 agonist in human.

• PD effects in human are observed with doses starting at 100 mg. At higher doses, more responders and greater amplitude of response are observed.

• These promising preclinical results and Phase 1 clinical data provide encouragement to further explore RO7020531’s therapeutic effect in chronic hepatitis B patients in combination with direct acting antiviral agents.
Doing now what patients need next