Therapeutic Efficacy of a TLR7 Agonist for HBV Chronic Infection in Chimpanzees

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Background

• TLR7 predominantly present in plasmacytoid dendritic cells.

• Stimulation induces IFN-α, immune stimulatory and select pro-inflammatory cytokines, and regulation of innate and adaptive immunity.

• GS-9620 is a orally available TLR7 agonist selective for induction of IFN-α and stimulatory cytokines.

• Induction of the innate immune response by GS-9620 has been characterized in monkeys, chimpanzees and humans.

• Approx. 6-fold less potent in chimpanzees in comparison to man.

• HBV infected chimpanzees were selected as the animal model for antiviral efficacy.
Acute Resolving HBV Infection in the Chimpanzee

4x0333 Acute HBV

serum titer  ALT  AST  GGT

Week

U/L

Lanford, et al., EASL 2011; Oral #1771
To determine an appropriate starting dose for efficacy studies in infected animals, a single oral dose evaluation of PK, PD and tolerability was performed in uninfected chimpanzees.

**IFN-α Induction @ 0.3 and 1 mg/kg**

- ▲ 0.3 mg/kg
- □ 1 mg/kg (A)
- ◇ 1 mg/kg (B)

**C\(_{\text{max}}\) GS-9620 vs IFNα**

N = 3 animals at 0.3 mg/kg, n =3 at 1 mg/kg (A), and n =4 at 1mg/kg (B).
ISG and Serum Cytokine Induction in Uninfected Chimpanzees

Pharmacodynamic responses in uninfected animals after a single oral GS-9620 dose of 1 mg/kg.

Mean of the peak fold increases are shown at 8 hrs post dosing at 1 mg/kg for n=7 animals.

Lanford, et al., EASL 2011; Oral #1771
PK and Efficacy Study Design

3 HBV chronically infected chimpanzees: Oral dosing three time per week

- HBV DNA, HBeAg and HBsAg
- ISGs in PBMC and Liver, Cytokine/Chemokine
- Lymphocyte activation markers
- Liver histology
- Safety parameters: CBC, blood chemistries, observations
# Baseline Characteristics of HBV Chronically Infected Chimpanzees

<table>
<thead>
<tr>
<th>Animal ID</th>
<th>Baseline HBV DNA</th>
<th>HBeAg</th>
<th>Anti-HBeAg</th>
<th>Anti-HBcAg</th>
<th>Sex</th>
<th>Duration of HBV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>4x0139</td>
<td>6.5x10^7</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>F</td>
<td>30 Years</td>
</tr>
<tr>
<td>4x0328</td>
<td>2.5x10^5</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>M</td>
<td>&gt; 24 Years</td>
</tr>
<tr>
<td>4x0506</td>
<td>1.6x10^4</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>F</td>
<td>&gt; 27 Years</td>
</tr>
</tbody>
</table>
Antiviral Response in High Titer Chimpanzee

4x0139

- Serum IU/mL (Cobas)
- Liver ge/μg

Day

Day

Day
Antiviral Response in Low Titer Chimpanzees

![Graph showing antiviral response in low titer chimpanzees](image-url)
Reduction in Serum HBsAg and HBeAg in High Titer Chimpanzee

4x0139

Viral Titer, HBeAg, HBsAg

Day

IU/mL

Percent of Pretreatment

Lanford, et al., EASL 2011; Oral #1771
Induction of ISG Transcripts in Liver

**IP-10**

Copy/µg

10^3 - 10^6

Day

1 mg/kg 2 mg/kg

**ISG15**

Copy/µg

10^5 - 10^8

Day

1 mg/kg 2 mg/kg

**ITAC**

Copy/µg

10^4 - 10^7

Day

1 mg/kg 2 mg/kg

**GAPDH**

Copy/µg

10^5 - 10^8

Day

1 mg/kg 2 mg/kg

Lanford, et al., EASL 2011; Oral #1771
Induction of ISG Transcripts in PBMC

IP-10

ISG15

ITAC

GAPDH
Serum Levels of Liver Enzymes: ALT, GGT & AST

4x0139 had a dosing holiday on Days 43, 45 and 47.
# Activation of Peripheral Blood Cells

<table>
<thead>
<tr>
<th>Cell Population</th>
<th>Marker</th>
<th>Fold Increase in Percent Positive Cells (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Lymphocytes</td>
<td>CD69</td>
<td>3-5 fold</td>
</tr>
<tr>
<td>CD8 T lymphocytes</td>
<td>CD69</td>
<td>2-5 fold</td>
</tr>
<tr>
<td></td>
<td>CD25</td>
<td>2-5 fold</td>
</tr>
<tr>
<td>CD4 T lymphocytes</td>
<td>CD25</td>
<td>2-4 fold</td>
</tr>
<tr>
<td>NK and NKT Cells</td>
<td>CD69</td>
<td>2-6 fold</td>
</tr>
</tbody>
</table>

Evaluated on Day -28 and 8 hours post dose on Days 7, 14, 25, 31, 45 and 57.
Conclusions

• Oral GS-9620 for 8 weeks reduced serum and liver viral DNA in all three HBV infected chimpanzees.

• The mean maximal reduction in serum viral load was 2.2 logs, with a duration of at least one log reduction from 64 days to >121 days.

• Reductions in viral load correlated with reductions in serum HBsAg in all three animals and with reduction of HBeAg in one animal.

• GS-9620 induced dose dependent increases in serum IFN-α, ISGs in PBMCs and liver, and activation of lymphocyte subsets: CD8+ T and NK cells.

• Increased liver enzymes were observed and returned to baseline by the end of the study.