THE S-ANTIGEN TRANSPORT-INHIBITING OLIGONUCLEOTIDE POLYMER (STOPS™) ALG-010133 DEMONSTRATES A FAVORABLE PRECLINICAL PROFILE FOR THE TREATMENT OF CHRONIC HEPATITIS B

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Background

Chronic Hepatitis B (CHB) viral infection is a global public health problem affecting over 290 million people. Current standard of care can effectively inhibit viral DNA replication but fails to reduce HBsAg. Nucleic acid polymers (NAPs) have been reported to reduce circulating HBsAg in patients with CHB by potentially affecting protein trafficking from the infected cell. We have identified STOPS™ compounds that contain several novel chemical features, providing enhanced potency in several HBV cell lines.

Methods

ALG-010133 was formulated in either phosphate buffered saline or water for injection. CD-1 mice and cynomolgus monkeys were dosed subcutaneously (SC), or by intravenous infusion (IV), in monkeys, to assess the pharmacokinetic properties of ALG-010133. Additionally, toxicokinetic analysis was conducted in mice and monkeys administered ALG-010133 with weekly SC (QW; 3 doses) over 2 weeks in toxicology studies.

Sustained exposure in liver following single SC dose in mice and monkey

Dose-related increase in liver exposure following weekly SC dosing

Species | Matrix | Dose (mg/kg) | Half-life (hour) | Cmax (µg/mL or µg/g) | AUC0-24 (µg•h/mL or µg•h) |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Plasma</td>
<td>5</td>
<td>6</td>
<td>0.1</td>
<td>0.8</td>
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<tr>
<td>Mouse</td>
<td>Liver</td>
<td>5</td>
<td>91</td>
<td>15.7</td>
<td>930</td>
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<td>Plasma</td>
<td>5</td>
<td>NC</td>
<td>4</td>
<td>42</td>
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<tr>
<td>Monkey</td>
<td>Liver</td>
<td>5</td>
<td>147</td>
<td>13</td>
<td>1,078</td>
</tr>
</tbody>
</table>

NC: Not calculated due to insufficient points post Cmax

• Rapid and high liver uptake was observed in mice and monkeys following single dose of ALG-010133
• ALG-010133 has a long half-life. Overall much higher exposure were seen in tissues compared to plasma
• Long half-life in the liver supports once weekly dosing in humans

Good bioavailability following single SC dosing in monkeys

Dose

\[
\begin{align*}
\text{Dose (mg/kg)} & \quad \text{Route} & \quad \text{Cmax (µg/mL or µg/g)} & \quad \text{AUC0-24 (µg•h/mL or µg•h)} & \quad \text{t1/2 (h)} & \quad \text{Vss (L/kg)} & \quad \text{F (±)} \\
5 & IV & 2 & 25.6 & 42.7 & 2.3 & - & - & 0.2 & - \\
5 & SC & 6 & 3.2 & 26.2 & 2.3 & - & - & 62 & - \\
50 & IV & 1 & 1.3 & 2.3 & - & - & - & - & - \\
50 & SC & 1 & 0.8 & 2.3 & - & - & - & - & - \\
100 & IV & 3 & 0.6 & 1.6 & - & - & - & - & - \\
100 & SC & 3 & 0.4 & 1.4 & - & - & - & - & - \\
200 & IV & 3 & 0.4 & 1.4 & - & - & - & - & - \\
200 & SC & 3 & 0.3 & 1.2 & - & - & - & - & - \\
\end{align*}
\]

† The no-observed-adverse-effect-level in both species was 50 mg/kg/dose, the highest dose tested

• Pooled monkey plasma (n=10) following SC dose at 5mg/kg were used for metabolite identification; metabolites were qualitatively identified using LC-HRMS

• The parent compound was the most abundant species in plasma; only trace levels of 5′-exonuclease cleavage products (5′-n-1 and 5′-n-2) were observed

Limited urinary excretion in monkeys

• Following single SC dose of ALG-010133 in monkeys at 100 or 200 mg, ALG-010133 was quantifiable in urine up to the 60–72 hours post-dose time point
• 4% and 9% of dose were recovered in urine within 72 hour of ALG-010133 dose at 100 and 200 mg, respectively

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Low potential for DDI

• ALG-010133 demonstrated a favorable safety profile

In 2-week repeat dose studies in mice and monkey following weekly SC administration, ALG-010133 was well tolerated to up to the highest dose tested of 50 mg/kg/dose

• There were no signs of change in serum chemistry or hematological parameters
• There was no evidence of adverse events in any species

• There were no adverse changes in hematology, serum biochemistry, coagulation parameters

• There were no observations adverse-effect level in both species was 50 mg/kg/dose, the highest dose tested

Conclusions

The combination of PK properties to enable SC administration along with a favorable safety profile allowed advancement of ALG-010133 into clinical development. ALG-010133 will be further evaluated as a potential treatment for CHB.

References


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