Preclinical Profile of ALG-125755, a GalNAc-siRNA Targeting HBV

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Aligos Therapeutics, Inc.
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Therapeutic Approaches to CHB Functional Cure

Aligos is developing CAM-E ALG-000184, siRNA ALG-125755 and liver targeting PD-L1 inhibitor
ALG-125755 Structure and Target Sequence

Homology to >9700 HBV Clinical Isolates

<table>
<thead>
<tr>
<th>GalNac siRNA</th>
<th>Gt A</th>
<th>Gt B</th>
<th>Gt C</th>
<th>Gt D</th>
<th>Gt E</th>
<th>Gt F</th>
<th>Gt G</th>
<th>Gt H</th>
<th>Gt I</th>
<th>Gt J</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALG-125755</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>99%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Homology: 0 mismatch (95%) + 1 mismatch (5%)

ALG-125755 targets a very conserved HBV site and utilizes proprietary stabilization chemistries.
ALG-125755 targets an essential region that is present in HBsAg mRNA produced from cccDNA and integrated DNA.
The Antisense Strand of ALG-125755 Demonstrates Activity in an Ago-2 Biochemical Assay

Ago-2 with antisense strand of ALG-125755 cleaves complementary HBV RNA at expected location

Antisense Strand of ALG-125755

Target HBV RNA

18 nt

10 nt

Antisense Strand of ALG-125755

Ago2: - - + + + + + -

Non-Target RNA

Target RNA

nt

- 20

- 18
In Vitro Activity of ALG-125903: The Unconjugated Form of ALG-125755

HepG2.2.15

EC$_{50}$ = 17.48 pM; CC$_{50}$ >1000 pM

HBV Infected Primary Human Hepatocytes

EC$_{50}$ = 5.58 pM; CC$_{50}$ >1000 pM

Unconjugated version of ALG-125755 showed pM EC$_{50}$ values in HBV cell models
ALG-125755 Demonstrated Potent Antiviral Activities vs. HBV Clinical Isolates
ALG-125755 In Vivo Activity in the AAV-HBV Mouse Model

ALG-125755 incorporating proprietary chemistries showed significant improvement over parental siRNA.
ALG-125755: In Vivo MOA Analysis at the End of Study

AAV HBV: 42 days post single dose of 5 mg/kg

Liver HBV RNA by Northern

Liver HBsAg by ELISA

Serum HBsAg by ELISA

ALG-125755 MOA: reduction of serum HBsAg was due to cleavage of HBV RNA in liver through RNAi
ALG-125755 demonstrates a more sustained reduction in HBsAg vs. competitor siRNAs

VIR-2218*

- Mean Log_{10} IU/mL HBsAg Reduction Relative to Day 0

- PBS, SC, Q2W, Day 0-70
- VIR-2218, 3 mg/kg, SC, Q2W, Day 0-70

ALG-125755

- Mean Log_{10} IU/mL HBsAg Reduction Relative to Day 0

- Vehicle, 5 mL/kg, SC, Q2W, Day 0-70
- ALG-125755, 5 mg/kg, SC, Q2W, Day 0-70
ALG-125755: PK-PD Correlation in Mouse

- For siRNA, $C_{avg}$ appears to be more relevant PK parameter for efficacious target.

- Only maximum HBsAg change from baseline was considered; sustained PD durability was not taken into consideration for the mouse PK/PD analysis.

- ALG-126144 is 3’ N-1 active metabolite.
ALG-125755: Single SC Dose PK at 5 mg/kg in Rat and Monkey

**Rat**

- Liver $C_{\text{max}}$ 64.8 µg/g and $T_{1/2}$ 6.8 days

**Monkey**

- Liver $C_{\text{max}}$ 38.4 µg/g and $T_{1/2}$ 26.4 days

ALG-125755 single SC injection in rat and monkey: high liver exposure and long liver half life
ALG-125755 showed no immune activation in cytokine release assays performed in PBMC from 8 donors.
ALG-125755 In Vitro Off Target Profile

- Experimentally investigated potential off targets identified by bioinformatics

<table>
<thead>
<tr>
<th>Human mRNA</th>
<th>0 MM</th>
<th>1 MM</th>
<th>2 MM</th>
<th>3 MM</th>
<th>4 MM</th>
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</thead>
<tbody>
<tr>
<td>ALG-125755 hits</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer No.</th>
<th>HepG2.2.15 25 pM (96 hour)</th>
<th>HepG2.2.15 250 pM (96 hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene 1</td>
<td>1</td>
<td>0.53±0.015</td>
<td>1.41±1.10</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.66±0.292</td>
<td>1.34±0.73</td>
</tr>
<tr>
<td>Gene 2</td>
<td>1</td>
<td>0.33±0.056</td>
<td>0.44±0.17</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.61±0.478</td>
<td>1.22±1.10</td>
</tr>
</tbody>
</table>

Note: The signals were normalized against control B2M gene expression.

- Unbiased RNAseq in HepG2.2.15 cell line: 10 nM, 1000x EC<sub>50</sub>

Unconjugated ALG-125755 10 nM

No cellular pathway affected

1 off target confirmed by 2<sup>nd</sup> independent experiment and qPCR
ALG-125755 FIH-enabling GLP Tox Studies

• Negative in the in vitro Ames and MNT studies
• Negative in rat MNT up to 2000 mg/kg
• No apparent changes in hemodynamic, ECG or respiratory parameters in monkeys or neurobehavioral findings in rats or monkeys up to 100 mg/kg, the highest dose tested
• Well tolerated in rat and monkey 5-week/6 dose repeat-dose tox studies with weekly subcutaneous doses of 0 (vehicle), 10, 30, 100 mg/kg/dose
  – The highest dose tested was the no observed adverse effect level (NOAEL) in both species

<table>
<thead>
<tr>
<th></th>
<th>NOAEL (mg/kg/dose)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>AUC&lt;sub&gt;0-24hr&lt;/sub&gt; (µg.hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>100</td>
<td>36</td>
<td>223</td>
</tr>
<tr>
<td>Monkey</td>
<td>100</td>
<td>17.5</td>
<td>271</td>
</tr>
</tbody>
</table>

Favorable nonclinical toxicology profile for ALG-125755
1) Confirmed ALN-HBV is hepatotoxic, VIR-2218 is not
2) ALG-125755 showed no evidence of hepatotoxicity as manifested by human ALT elevation

ALG-125755: Further De-risked Preclinically in PXB Mice with Humanized Livers

- Vehicle
- 50 mg/kg ALG-755
- 48.3 mg/kg ALN-HBV
- 50 mg/kg VIR-2218
Short Interfering Nucleic Acid ALG-125755
Discovery and Advancement of a Differentiated siRNA

- siRNAs have demonstrated clinical validation in CHB infected patients

- We have designed our siRNA sequences using our proprietary technology and liver targeting conjugation to maximize in vitro and in vivo potency
  - Proprietary chemistries discovered to increase potency and stability/duration of action
  - Exclusive license to GalNAc technology applicable for liver targeting across oligo modalities

- Our siRNA approach may have safety, stability and potency advantages vs. competitor siRNAs

- Dosing in healthy volunteers was initiated in October 2022, dosing in CHB patients in December 2022

ALG-125755 is differentiated from potential competitors. HV and CHB patient dosing started Q4 2022
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