Development of a Best-in-Class HBV ASO, ALG-020572, for the Treatment of Chronic Hepatitis B

- Potential for Combination with other Anti-HBV Agents
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Disclosure

Jin Hong
I disclose the following financial relationship(s) with a commercial interest:
• Aligos Therapeutics, Inc.
Our CHB Portfolio

- Potentially best-in-class drug candidates directed against clinically validated targets with the potential to achieve high rates of functional cure following finite therapy
  - S-antigen Transport-inhibiting Oligonucleotide Polymers (STOPS™)
  - Capsid assembly modulators (CAMs)
  - Oligonucleotides (ASO, siRNA)
Antisense Oligonucleotide Platform Technology
- successfully addressing the hepatotoxicity associated with LNA ASO’s

GalNac4

2’-Modified

Wing:
High Stability,
High Binding

Gap:
RNaseH

2’-Deoxy

Wing:
High Stability,
High Binding

8-Amino-A

8-Amino-G

5-HO-C

2-Thio-T

LNA

Snp BNA (L.una)

AmNA (L.una)

Snp BNA (L.una)

4mNA (L.una)

LNA

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AAV-HBV Mouse Model: ASO Wing Modification with 3rd Gen BNA Improved Potency and Reduced Liver Toxicity
AAV-HBV Mouse Model: ASO Gap Nucleobase Modification Significantly Reduced Liver Toxicity while Maintaining Potency
ALG-020572 HBV ASO Derived from Aligos’ Platform

Genotypic Coverage: % Homology Among >8000 Clinical isolates

<table>
<thead>
<tr>
<th>Genotype</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
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</thead>
<tbody>
<tr>
<td>ALG-020572 (S)</td>
<td>98%</td>
<td>100%</td>
<td>99%</td>
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ALG-020579, Unconjugated form of ALG-020572 inhibits HBsAg release in HepG2.2.15 cells

ALG-020579

EC$_{50}$ = 15.4 nM
CC$_{50}$ >100 nM

Adapted from Lamontagne et. al. Hepatoma Res 2016;2:163-186
AAV-HBV Mouse Model: ALG-020572 Demonstrated Significant In Vivo Activity and Dose-response

AAV-HBV: Serum HBsAg
Mean ± SEM

No ALT Elevation Observed
ALG-020572 Conjugated with Aligos GalNac4: Transportation and Processing in Human Hepatocyte Systems

- Human System: ASGPR, esterase and RNaseH1

**Receptor Mediated Uptake**

- Fresh PHH from CHB FRG Mouse
- HBsAg

**Graph:**
- ALG-020572 (S) Analog
- HBsAg EC50 = 27 nM

**Receptor Mediated Uptake**

- Revitalized PHH in 3-D Chip
- HBsAg

**Graph:**
- ALG-020572 (S) Analog
- % of HBsAg (normalized to day 9)
AAV-HBV Mouse Model: HBV ASO’s ALG-020572 (S) and ALG-020576 (X) Exhibited Additivity in Combination

Lower Dose
6X3 mg/kg Individual
6x(1.5+1.5)mg/kg Combo

Higher Dose
6X10 mg/kg Individual
6x(5+5)mg/kg Combo

No ALT Elevation Observed
ALG-020572 Exhibited Additivity when Combined with HBV siRNA

Additive in HepG2.2.15 Assay
Synergy Volume = 19.3 µM²%

ASO: unconjugated form of ALG-020572
unconjugated form of siRNA lead

ASV-HBV Mouse Model Serum HBsAg

HBV ASO

HBV siRNA

G 01: Vehicle, 5 mL/kg, SC, Q3W, Day 0 ~ 42
G 06: ALG125097, HBV siRNA 3 mg/kg, SC, Once
G 18: ALG-020572, HBV ASO 4X3 mg/kg, SC, QW
G 20: ALG-020572 HBV ASO 4X3mg/kg SC QW;
+ ALG-125097 HBV siRNA 3mg/kg SC Once

No ALT Elevation Observed

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ALG-020572 Analog Exhibited Strong Synergy when Combined with ALG-010133 STOPS™ Compound

Unconjugated Analog of ALG-020572 X ALG-010133
Synergy Analysis (95% confidence interval)

Strong Synergy
Synergy Volume = 291.6 µM²%
No Cellular Cytotoxicity
AAV-HBV Mouse Model: ALG-020572 Analog Showed Additivity when Combined with ETV and HBV CAM, ALG-000184 Analog

No ALT Elevation Observed
Key Takeaways

• Aligos’ ASO platform technology significantly improves the preclinical safety profile of ASO’s

• HBV ASO ALG-020572 derived from the platform demonstrates a good in vivo potency and safety profile in the AAV-HBV mouse model

• ALG-020572 or its unconjugated form demonstrated additive to synergistic activity when combined with other anti-HBV agents in vivo or in vitro
Acknowledgements

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