Oligonucleotide Based Approaches to the Treatment of Chronic Hepatitis B

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Chronic Hepatitis B – A Large Unmet Medical Need

• Epidemiology*
  – Most common chronic viral infection in the world
  – 290 million chronic carriers
    › 94 million cases in China, >2 million cases in the US, 15 million cases in the EU, >2 million cases in Japan
  – 30 million new infections every year
  – 884,000 people (2 per minute) die every year from HBV complications

• Despite a prophylactic vaccine and available therapies
  – Hepatitis B is the primary cause of liver cancer worldwide
  – Mortality associated with liver cancer and cirrhosis continues to increase

• Current therapy (nucleos(t)ide analogs) lowers HBV DNA on treatment, but requires long-term treatment and rarely results in a “functional cure” (i.e., undetectable HBV DNA, HBsAg after finite treatment**)

*Data summarized from the Hepatitis B Foundation (hepb.org) and the World Health Organization (who.int, euro.who.int) accessed July 2020.
Therapeutic Approaches to CHB Functional Cure

Inhibit Viral Replication

Lower Antigen Burden

Boost Immune Response

Nucleoside and Nucleotide Analogs (e.g., ENT, TDF)

Interferon

PEG-IFNα

Viral Entry

Viral Capsid Assembly

Viral Secretion

Antigen Secretion (HBsAg)

Endoplasmic Reticulum

OLIGONUCLEOTIDES

Infected Hepatocyte

Cam

pgRNA

mRNA

cccDNA

rcDNA

Host Polymerase

Viral Polymerase

Integrated HBV/DNA

Nucleus

CD8+

NK

B-Cell

T-Cell exhaustion

Cytokines

DC

MO

PD-1/PD-L1

Treg

Interferons

Metabolic Regulation

Therapeutic Vaccine

Innate Immunity

0701 Arginase

0701 Arginase
Chronic Hepatitis B and Functional Cure
Outcome Determined by Balance Between Virus and Host Immune Response

Chronic Hepatitis B

- Robust Viral Replication (High HBV DNA & RNA Levels)
- Suppression of HBV-specific immune response (high HBsAg levels)

Therapeutics Tip the Balance

- Direct Acting Antivirals
- Oligonucleotides, PD-L1, IFN

Functional Cure

- No viral replication (undetectable HBV DNA & RNA)
- Restore HBV-specific immune response (undetectable HBsAg levels)

Functional Cure: Sustained loss of HBsAg with or without anti-HBs antibody seroconversion
Lowering S-Antigen Burden with Oligonucleotides

- ALG-010133, a novel LNA containing poly-AC 40-mer “STOPS” (poster at this roundtable)
- ALG-020572, a novel Luxna modified GalNAc conjugated antisense oligonucleotide
- ALG-125755, a novel GalNAc conjugated small interfering RNA
**Antisense Oligonucleotides and Small-Interfering RNAs**

**RNA interference (RNAi)**
- Synthetic siRNA
- Strand Separation
- Complementary Pairing
- Cleavage
- mRNA Degradation

**Antisense oligonucleotides (ASOs)**
- ASO (DNA)
- All PS* Wings (LNA) GAP (DNA)
- mRNA-Antisense Duplex
- RNase H1 Recognizes Duplex
- RNase H1 Enzyme Cleaves mRNA

- Long duration of suppression with plateau
- Slow onset with not a clear dose response
- Infrequent dosing

- Deep suppression with dose response
- Fast onset with loading strategy
- Relatively frequent dosing

*PS = Phosphorothioate.
The hepatitis B viral genome has an overlapping reading frame:

mRNA coding for multiple products can be silenced using a single oligonucleotide construct

ALT elevations have been observed clinically for X region targeting siRNA constructs advanced by Arbutus* and Alnylam**
Lowering S-Antigen Burden with Oligonucleotides

- ALG-020572, a novel Luxna modified GalNAc conjugated ASO
Discovery of ASO ALG-020572

• Aligos has utilized our bioinformatics platform in the selection and optimization of novel ASO constructs, to maximize coverage and minimize off-target potential

• We optimized our sequences using our proprietary Luxna Biotech chemistries to enhance in vitro potency, stability and, potentially, safety
  – Luxna XNA are 3rd generation nucleotides and may improve nuclease resistance and reduce hepatotoxicity

• Potent ASOs were conjugated to our proprietary GalNAc ligands for targeted liver delivery

• This approach has led to the selection of our ASO drug candidate ALG-020572
Luxna Next Generation XNA Chemistries for ASO

- XNA chemistry (Professor Obika)
  - scpBNA, AmNA, GuNA (wing)
  - 8-amino-A/G, 5-OH-C, 2-Thio-T (gap)

- Potential advantages over earlier LNA technologies
  - Improved base specific hybridization
    - Enhanced potency
  - Higher nuclease resistance
    - Enhanced stability
  - Modulation of hydration pattern
  - Reduction in hepatotoxicity

GalNAc, scpBNA-5-Me-C and 5-OH-C Monomers
Large Scale Syntheses Fully Enabled

Routes established for multi-kg syntheses of key non-commercially available monomers
In Vitro and In Vivo Potency
Effect of Individual Luxna Modifications on the Parent Sequence

<table>
<thead>
<tr>
<th>Antisense Oligonucleotide</th>
<th>Modification</th>
<th>In Vitro EC\textsubscript{50} in HepG2.2.15</th>
<th>In Vivo (GalNAc Conjugated) HBsAg Reduction (AAV Mouse)</th>
<th>ALT Fold Increase (AAV Mouse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5' Unmodified sequence of ALG-020572 3'</td>
<td>11.5 nM</td>
<td>1 log</td>
<td>3X</td>
<td></td>
</tr>
<tr>
<td>5' 3'-scpBNA-5-Me-C modification 3'</td>
<td>13.4 nM</td>
<td>1 log</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>5' 5-OH-C modification 3'</td>
<td>NT</td>
<td>1 log</td>
<td>No increase</td>
<td></td>
</tr>
<tr>
<td>5' ALG-020572 parent sequence with modifications 3'</td>
<td>12.6 nM</td>
<td>1.5 log</td>
<td>No increase</td>
<td></td>
</tr>
</tbody>
</table>

Better in vivo potency for the wing and gap optimized ASO, without ALT elevation
ALG-020572
Clinical Development

• GLP toxicology studies
  – Well tolerated at the highest doses tested, no safety signals identified

• Phase 1a - single ascending doses in healthy volunteers
  – Considered safe up to the highest dose tested, 480 mg sub-cutaneous

• Phase 1b - multiple ascending doses in CHB infected subjects*
  – Starting dose of 210 mg sub-cutaneous, planned for 7 doses
  – Clear evidence of target engagement, antiviral effect
  – Poorly tolerated after dosing for 4-29 days
    › Multiple subjects experienced ALT >10X ULN → concerning of DILI**

• Viral kinetic, PK and additional data will be reported at a later conference***

ALG-020572 ASO program was discontinued following the Phase 1b safety observations

*Gane, E. et al., EASL 2022.
**DILI = Drug Induced Liver Injury.
***AASLD 2022, abstract accepted.
Aligos Early Oligonucleotide Programs
Lessons Learned

• STOPS, ALG-010133*
  – 100-fold more potent in vitro than competitor REP-2139, cell-based assay (transfection)
    › No suitable in vivo efficacy model has been established
  – Compound was safe and well tolerated in GLP studies
  – Compound was safe and well tolerated in subjects, both health volunteers and CHB
  – No antiviral response seen up to the highest dose tested (400 mg SC, QW, 12-weeks)

• ASO, ALG-020572**
  – Potent in both in vitro and in vivo preclinical assays
  – Safe and well tolerated in GLP studies and in healthy volunteers
  – Clear evidence of target engagement and antiviral effect
  – Poorly tolerated in CHB subjects following multiple doses

There is a significant need for better safety (ASO) and efficacy (STOPS) models for HBV oligonucleotides

*IRT / IS3NA 2022, Santhosh Thatikonda poster.  
**AASLD 2022, abstract accepted.
Lowering S-Antigen Burden with Oligonucleotides

- ALG-125755, a novel GalNAc conjugated siRNA
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
  - Bioinformatics approach utilized to achieve broad coverage and minimize off-target potential
  - Proprietary patterns 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

- CTA filing and first-in-human dosing is on-track – H2 2022

ALG-125755 is differentiated from potential competitors. CTA submission planned in Q3 2022
Aligos Screening Funnel for siRNA Advancement

Full Bioinformatics, Synthesis

HBV Activity in Cell-Based HepG2.2.15 Assay

In vivo Efficacy/Tox: AAV-HBV Mouse

Proprietary Designs + Chemistries
AAV-HBV, Human PBMC

Rat and Monkey PK and DRF

Clinical Candidate
ALG-125755

- Synthesis of 200 chemically modified siRNA
- Scale-up of 40 siRNA GalNAC conjugated
- Optimization of 4 sequences
- Significant scale-up for toxicology studies

2 designs, 100 Sequences

~40 Seq (S & X)

4 Seq (S & X: 2leads & 2 backups)

5 siRNA (3X, 2S) for Rat DRF
1 siRNA Monkey DRF

DRF = Dose Range Finding.
# ALG-125903 (Unconjugated Form of ALG-125755)
Genotype Coverage and Off-Target Analysis

## Table

<table>
<thead>
<tr>
<th>siRNA</th>
<th>Genotype A</th>
<th>Genotype B</th>
<th>Genotype C</th>
<th>Genotype D</th>
<th>Human Off-Target 0 MM</th>
<th>Human Off-Target 1 MM</th>
<th>Human Off-Target 2 MM</th>
<th>Human Off-Target 3 MM</th>
<th>Human Off-Target 4 MM</th>
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<tbody>
<tr>
<td>ALG-125755</td>
<td>98.3%</td>
<td>99.8%</td>
<td>99.9%</td>
<td>99.7%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>VIR-2218</td>
<td>94.3%</td>
<td>99.4%</td>
<td>99.9%</td>
<td>96.6%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>133</td>
</tr>
</tbody>
</table>

Genotype coverage includes 0 or 1 mismatch. MM = mismatch

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Superior genotype coverage with minimal potential for off-target complications

[Diagram of ALG-125903 siRNA with annotations for sense and antisense strands]
ALG-125755
Potent Inhibition of HBsAg Release in Multiple Cell Lines

- Inhibition of HBsAg release by ALG-125903 (unconjugated ALG-125755) was measured in HepG2.2.15 cells and HBV-infected primary human hepatocytes.
  - Cytotoxicity is not observed up to the highest concentrations tested.

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC\textsubscript{50} HepG2.2.15\textsuperscript{a} (pM)</th>
<th>CC\textsubscript{50} HepG2.2.15\textsuperscript{a} (pM)</th>
<th>EC\textsubscript{50} HBV-infected PHH\textsuperscript{b} (pM)</th>
<th>CC\textsubscript{50} HBV-infected PHH\textsuperscript{b} (pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALG-125903</td>
<td>10.8±4.2</td>
<td>&gt;1000</td>
<td>9.1±1.5</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

\textsuperscript{a} A commonly used HBV model that contains integrated Genotype D HBV genomes.

\textsuperscript{b} The PHH cells are infected at 200 MOI (ge) 4 days prior to siRNA transfection with live genotype D laboratory strains from HBV-infected cells.

ALG-125903 exhibits picomolar EC\textsubscript{50} values for inhibition of HBsAg release in HepG2.2.15 and HBV-infected PHH cells.
ALG-125755 demonstrates deep and sustained reductions in HBsAg following multiple doses.*

Applying Lessons Learned
Additional Studies in the PXB Mouse Model

• Repeat dose studies in the PXB mouse model
  – Humanized liver allows assessment of safety

• Human ALT readout throughout the study
  – Doses on day 1, 22, 29, 36 and 43
    › Vehicle control
    › ALN-HBV at 48.3 mg/kg (X, ALT in humans*)
    › VIR-2218 at 50 mg/kg (X, continuing in Phase 2**)
    › ALG-125755 at 10 and 50 mg/kg

• Interim data up to day 39 is supportive of continued ALG-125755 development
  – S-targeting siRNA shows no significant ALT elevations relative to X-targeting siRNA

ALG-125755 appears safe and well-tolerated in the PXB mouse with no significant ALT elevations observed

% Change in Human ALT from pre-dose day 1 (Interim Data)

*ALN-HBV was discontinued for safety, see Maler, M.A. et al., Nucleic Acid Research, 2022, 1.
**VIR Corporate Presentation, August 9th, 2022.
ALG-125755 + ALG-020572 (Unconjugated)
In Vitro Combination Shows Synergy with no Cytotoxicity

The synergy volume for the interaction between ALG-020579 and ALG-125903 was 46.01 μM²% suggesting a synergistic interaction
ALG-125755 + ALG-020572 (GalNAc Conjugated)
In Vivo Combination Study in the Mouse AAV-HBV Model

The combination of our siRNA and ASO delivers rapid, potent suppression of HBsAg in vivo.
Chronic Hepatitis B
Approach to the Development of a CHB Functional Cure

**Combination Protocol**

Multiple combinations of CAM, Oligonucleotide and PD-L1 +/- SOC in patients with CHB x 24-48 week treatment

**MOA #1**
- Healthy Volunteers
- Patients

**MOA #3**
- Healthy Volunteers
- Patients

**Phase 1a**
- Multipart Umbrella Protocols

**Phase 1b**
- Platform Protocol

**Phase 2**
- Safety + PK (DNA, RNA, HBsAg)
- Safety + Efficacy (Functional Cure)

**Phase 3**
- Confirmatory (Functional Cure)

**Pivotal Trial(s)**

CAM = Capsid Assembly Modulator; CHB = Chronic Hepatitis B; DNA = Deoxynucleic Acid; HBsAg = Hepatitis B Surface Antigen; MOA = Mechanism of Action; PD = Pharmacodynamics; PD-L1 = Programmed Death Ligand 1; PK = Pharmacokinetics; RNA = Ribonucleic Acid; SOC = Standard of Care.
Aligos Therapeutics Summary

• Multiple oligonucleotide modalities have been advanced as potential components of a functional cure for CHB
  › STOPS (ALG-010133) discontinued for efficacy
  › ASO (ALG-020572) discontinued for safety
  › siRNA (ALG-125755) projected to advance into the clinic in 2H 2022

• Lessons learned
  – Better preclinical models are needed to reliably predict safety (ASO) and efficacy (STOPS)

• Small molecule modalities are also advancing
  – Class-II CAM (ALG-000184) dosing in Phase 1b – best in class data to date
  – PD-L1 and CAM-I programs are advancing toward candidate selection

• Great potential remains to develop a combination regimen to achieve a functional cure for chronic hepatitis B
Acknowledgements to the Aligos Team and Our Collaborators

• Project and Scientific Leadership
  – Leonid Beigelman, Lawrence Blatt, Julian Symons, Sushmita Chanda, Jin Hong, Saul Martinez Montero, Vivek Rajwanshi, Santhosh Thatikonda, Dinah Misner, Kusum Gupta, John Fry, Tse-I Lin, Megan Fitzgerald

• Collaborators
  – Luxna Biotech (Professor Satoshi Obika, Osaka University), AM Chemical (Dr. Andrei Guzaev)