Combination Approaches Towards a Functional Cure for Chronic Hepatitis B

Lawrence M. Blatt, PhD
Founder, CEO and Chairman
HEP DART December 7th, 2021
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Therapeutic Approaches to CHB Functional Cure

- **Lower Antigen Burden**
- **Inhibit Viral Replication**
- **Boost Immune Response**
## Therapeutic Approaches to CHB Functional Cure

### Lower Antigen Burden

- **STOPS (ALG-010133)**
  - Phase 1b clinical trial ongoing in CHB patients
  - Topline data from Cohorts 1-3 anticipated in H1 2022

- **ASO (ALG-020572)**
  - Phase 1a clinical trial ongoing in healthy volunteers
  - Anticipate dosing in CHB patients in Q1 2022

- **siRNA (ALG-125755)**
  - On track to advance into the clinic in 2022

### Inhibit Viral Replication

- **Class-II CAM (ALG-000184)**
  - Phase 1b clinical trial ongoing, currently dosing in 10 mg cohort
  - In HBeAg negative subjects at 50 and 100 mg QD over 28-days
    - HBV DNA <LLOQ in ≥75% of subjects
    - HBV RNA <LLOQ in 100% of subjects
  - In HBeAg positive subjects at 100 mg QD over 28-days
    - >4-log₁₀ drop in HBV DNA (IU/mL)
    - >3-log₁₀ drop in HBV RNA (copies/mL)

### Boost Immune Response

- **PD-L1 Small Molecule**
  - Multiple novel series discovered
  - Biochemical and cell-based potency established

- **Peg-IFN (SOC)**
  - Readily available

- **Class-I CAM**
  - Multiple novel non-HAP series discovered

- **Nucleos(t)ides (SOC)**
  - Readily available

Aligos is poised to begin Phase 2 explorations of fully owned combinations to enable functional cure.
Lowering Antigen Burden

- ALG-010133 (STOPSTM)
- ALG-020572 (ASO)
- ALG-125755 (siRNA)
ALG-010133*
Lead STOPS Molecule

Significantly greater potency** vs. reference Poly-AC oligonucleotide***

![Dose-response curves](image)

**Hong et. al., AASLD (2019), poster #0689.
***ALG-010004 has an identical oligonucleotide sequence as REP 2139. A. Vaillant, Antiviral Research 133 (2016) 32.

Proprietary chemistry, extensive structure activity relationship (SAR) effort identified STOPS
~100-fold improvement in potency vs. NAPs
Enables subcutaneous administration, may widen therapeutic index
**ALG-010133 Phase 1 Study in HV**

**Study Design**

**Single/Multiple Ascending Dose (SAD/MAD) study in HV**

N=72; n=8 per Cohort, n=6 ALG-010133, n=2 Placebo

Single (SAD) or three weekly subcutaneous (SC) doses (MAD)

- **SAD**
  - Follow-up
  - Safety and PK of single doses of 20, 50, 75, 125, 160 and 200* mg

- **MAD**
  - Follow-up
  - Safety and PK of 3 doses of 120 and 180 mg

*Dosing in HV complete*
**ALG-010133 Phase 1 Study in HV**

**PK Data**

Doses ≥125 mg approach linearity; low-to-moderate intersubject variability; no accumulation

Doses ≥120 mg anticipated to have antiviral activity

*All doses used 100 mg/mL solution except 2nd 200 mg cohort, which used 200 mg/mL solution.

Gane et al., EASL 2021.
ALG-010133 Phase 1 Study in HV

Safety

• No serious adverse events (SAEs)

• Treatment emergent adverse events (TEAEs)
  – No TEAEs led to study drug discontinuation
  – Injection site reactions (ISRs)
    › Occurred in ~19% of ALG-010133-treated subjects
      • Similar to ISR rate for other oligonucleotides (ASO, siRNA, etc.)*
      › Generally characterized by localized erythema that was mild to moderate in severity and resolved over time. One SAD ISR was considered severe based on surface area criteria (>100 cm²)

• No clinically concerning laboratory, ECG, vital sign or physical examination findings

Single, multiple ALG-010133 doses generally well tolerated in HV
Prophylactic topical steroids are being used in CHB subjects to potentially mitigate ISRs

Gane et. al., EASL 2021.
*Van Meer et al., BJCP, 2016.
**ALG-010133**  
**Phase 1b Study in CHB Subjects**

**Multiple Doses in CHB Subjects**
NA Suppressed (DNA < LLOQ), HBeAg neg or pos, HBsAg >100 IU/mL  
Up to 6 cohorts (n=10 per Cohort; n=8 ALG-010133, n=2 Placebo)  
Up to 12 weekly SC doses  
Endpoints: PK, safety, antiviral activity (e.g., HBsAg)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Endpoint data collected throughout, including</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=8</td>
<td>ALG-010133 + NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>N=2</td>
<td>Placebo + NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

1\textsuperscript{st} (120 mg) and 2\textsuperscript{nd} (200 mg) cohorts fully enrolled; 3\textsuperscript{rd} cohort (400 mg) enrolling, dosing  
Dose range finding study: target mean HBsAg reduction ≥1 log\textsubscript{10} IU/mL (similar to REP 102 at Week 10)
Antisense Oligonucleotides and Small-Interfering RNAs

RNA interference (RNAi)

- Synthetic siRNA
- Strand Separation
- Complementary Pairing
- Cleavage
- mRNA Degradation

Antisense oligonucleotides (ASOs)

- mRNA-Antisense Duplex
- RNase H1 Recognizes Duplex
- RNase H1 Enzyme Cleaves mRNA

Aligos is agnostic to oligonucleotide modality

*PS = Phosphorothioate

Dose dependent activity of ALG-020572 correlates with liver exposure

*ALG-020579 is the unconjugated form of ALG-020572 following GalNAc cleavage.

Gupta et al., AASLD 2021.
ALG-020572 demonstrates significantly improved efficacy in vivo vs. a competitor ASO.
ALG-020572
Phase 1a/b Clinical Trial Design

**Part 1: SAD (HV)**
Multiple Cohorts
Each Cohort - 6 Active: 2 Placebo

**Part 2: VS CHB patients**
Multiple Cohorts
Each Cohort - 6 Active: 2 Placebo

<table>
<thead>
<tr>
<th>Day</th>
<th>Loading Doses</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
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<tr>
<td>4</td>
<td></td>
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<tr>
<td>8</td>
<td></td>
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<td>11</td>
<td></td>
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<tr>
<td>15</td>
<td></td>
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<tr>
<td>22</td>
<td></td>
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<tr>
<td>29</td>
<td></td>
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</tbody>
</table>

Trial is ongoing – currently dosing in Healthy Volunteers
Phase 1 target mean HBsAg reduction: ≥1 log_{10} IU/mL
ALG-125755 demonstrates significantly improved efficacy in vivo vs. a competitor siRNA
The combination of our siRNA and ASO delivers rapid, potent and durable suppression of HBsAg in vivo
Inhibiting Viral Replication

- ALG-000184 (Class-II CAM)
- ALG-005398 (Class-I CAM)
**ALG-000184**

**Phase 1 Study in CHB Subjects**

**Multiple Doses in Currently Not Treated/Treatment Naïve CHB Subjects**

- HBV DNA > 2000 IU/mL, HBeAg Negative or Positive
- Up to 6 cohorts (n=10 per Cohort, n=8 ALG-000184, n=2 Placebo)
- 28 daily oral doses
- Endpoints: PK, safety, antiviral activity (e.g., DNA, RNA)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>Endpoint data collected throughout, including</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline, Week 4, Week 12</td>
</tr>
<tr>
<td>N=8</td>
<td>ALG-000184</td>
<td>No treatment</td>
</tr>
<tr>
<td>N=2</td>
<td>Placebo</td>
<td>No treatment</td>
</tr>
</tbody>
</table>

Complete 28-day data available in Cohorts 1 (100 mg in HBeAg-), 2 (50 mg in HBeAg-), and 4 (100 mg in HBeAg+).
## Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 HBeAg Neg (100 mg/placebo)</th>
<th>Cohort 2 HBeAg Neg (50 mg/placebo)</th>
<th>Cohort 4 HBeAg Pos (100 mg/placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age*, years</td>
<td>44.7 (2.9)</td>
<td>42.7 (2.8)</td>
<td>30.2 (2.4)</td>
</tr>
<tr>
<td>% Male</td>
<td>60</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>% Asian</td>
<td>10</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>BMI*, Kg/m²</td>
<td>26.7 (1.8)</td>
<td>24.3 (1.7)</td>
<td>21.8 (1.0)</td>
</tr>
<tr>
<td>ALT* IU/L</td>
<td>31 (8)</td>
<td>27 (5)</td>
<td>35 (6)</td>
</tr>
<tr>
<td>HBV DNA* (log₁₀ IU/mL),</td>
<td>4.2 (0.3)</td>
<td>4.7 (0.4)</td>
<td>8.1 (0.3)</td>
</tr>
<tr>
<td>HBsAg* (log₁₀ IU/mL),</td>
<td>3.4 (0.2)</td>
<td>3.0 (0.2)</td>
<td>4.5 (0.1)</td>
</tr>
<tr>
<td>Genotype A/B/C/D (N)</td>
<td>1/1/0/8</td>
<td>1/6/1/2</td>
<td>0/3/6/0**</td>
</tr>
</tbody>
</table>

*Mean (SEM). **1 unknown.
ALG-000184
Safety in CHB Subjects (Cohorts 1, 2 and 4)

- Serious adverse events: 1 (unrelated)
  - Subject with a history of sciatica experienced mild back pain resulting in brief hospitalization for pain management

- TEAEs
  - Leading to discontinuation: none
  - Generally mild or moderate, except three Grade 3 ALT elevations, all of which had onset post dosing and were not assessed as drug toxicity by the study ALT Flare Committee

- No concerning laboratories, EKGs, or vital signs

100, 50 mg ALG-000184 x 28 days was well tolerated in CHB subjects regardless of HBeAg status
PK profile in CHB comparable to HVs: linear, with minimal accumulation following oral daily dosing
ALG-000184
Day 28 Antiviral Activity* in CHB Subjects (Cohorts 1, 2 and 4)

50-100 mg ALG-000184 lowers HBV DNA by ~3-4 log10 IU/mL, RNA by ~1.5-3 log10 copies/mL
≥75% of HBeAg negative subjects’ DNA, RNA <LLOQ

*Roche COBAS HBV DNA ASSAY (LLOQ = 10 IU/mL).
Cohorts 1 and 2: Gane et. al., AASLD 2021.
Class-I Capsid Assembly Modulators

- Class I capsid assembly modulators are orally bioavailable small molecules that decrease HBsAg in the AAV-HBV mouse model

- Publicly disclosed Class-I CAMs are in the heteroaryl pyrimidine (HAP) class
  - GLS4 and RG7907 are two clinically reported entries with this structural motif
  - HAPs have several potential drawbacks related to safety
    - HBc dependent cell death of infected hepatocytes in vitro
    - ALT flare in animal models in vivo

- Aligos has discovered and optimized multiple non-HAP class-I CAM series
  - Proof of concept in HBV AAV animal model with ALG-005398
    - Significant reductions in HBV DNA, HBeAg and HBsAg without observation of ALT increases
ALG-005398
Proof of Concept in the AAV-HBV Mouse Model

- ALG-005398 potency in HepG2.117 cells
  - Reduction in HBV DNA
    - EC$_{50}$ = 3.4 nM
    - EC$_{90}$ = 10.6 nM

- Demonstration of class-I CAM properties
  - Formation of large aberrant capsids

ALG-005398 is a potent, non-HAP class-I CAM that reduces HBsAg and other antigens in vivo.
Boosting the Immune Response

- ALG-093453 (PD-L1 SM)
PD-L1 Small Molecule

• Exhaustion of HBV specific T-cells contributes to the persistence of CHB

• Proof of concept in CHB with anti-PD1 antibodies has been established
  – Multiple clinical studies have demonstrated quantitative reductions in HBsAg in CHB infected patients

• Aligos has discovered several potent series of small molecule PD-L1 inhibitors

• ALG-093453 is a novel small molecule PD-L1 inhibitor
  – Biochemical and cell-based potency established
**ALG-093453**

**PD-L1 Small Molecule**

**Biochemical Potency**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>INCB86550</th>
<th>ALG-093453</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1/PD-L1 IC50 (nM)</td>
<td>0.16</td>
<td>0.011</td>
<td>0.016</td>
</tr>
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**Cellular Activity**

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<tr>
<td>T cell activation EC50 (nM) (Emax % to PDL1 Abs)</td>
<td>3.5 (125)</td>
<td>8.6 (115)</td>
<td>1.5 (143)</td>
</tr>
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</table>

**HBV Positive Donor**

**ALG-093453 activates HBV specific T cells with low nM potency similar to nivolumab and durvalumab**
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Acknowledgements

Thanks to the entire Aligos and Emory team!