Brief History of RNA Interference

1996
First description of dsRNA as a trigger for gene specific silencing and termed RNAi

2002
First in vivo gene silencing with RNAi in mouse

2006
Fire and Mello awarded Nobel Prize for discovery of RNAi

2008
Proof of concept for use of an RNAi therapeutic in humans

2017
Positive Phase III data reported for Patiseran in Hereditary ATTR (hATTR) Amyloidosis Patients
## Current Development Landscape for RNAi in HBV

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company Name</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB-1467</td>
<td>Arbutus</td>
<td>Phase II</td>
</tr>
<tr>
<td>GalNAc RNAi</td>
<td>Arbutus</td>
<td>Preclinical</td>
</tr>
<tr>
<td>ARO-HBV</td>
<td>Arrowhead</td>
<td>Preclinical</td>
</tr>
<tr>
<td>DCR-HBV</td>
<td>Dicerna</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
## Significant Opportunity to Improve Cure Rates
Approved Therapies Show a Cure is Possible But Result in <5% Cure Rate

### Relative Efficacy of Approved HBV Therapies

<table>
<thead>
<tr>
<th></th>
<th>Entecavir$^{1,2}$</th>
<th>Tenofovir$^{3}$</th>
<th>PEG-IFN α-2a$^{4,5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg positive</strong></td>
<td>n = 354</td>
<td>n = 176</td>
<td>n = 271</td>
</tr>
<tr>
<td>HBV DNA undetectable</td>
<td>67%</td>
<td>76%</td>
<td>25%$^{a}$</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>21%</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>68%</td>
<td>68%</td>
<td>39%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>2%</td>
<td>3.2%</td>
<td>2.9%$^{b}$</td>
</tr>
<tr>
<td><strong>HBeAg negative</strong></td>
<td>n = 325</td>
<td>n = 250</td>
<td>n = 177</td>
</tr>
<tr>
<td>HBV DNA undetectable</td>
<td>90%</td>
<td>93%</td>
<td>63%$^{a}$</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>78%</td>
<td>76%</td>
<td>38%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0.3%</td>
<td>0%</td>
<td>0.6%$^{b}$</td>
</tr>
</tbody>
</table>

Results at 48 weeks
$^{a}$ HBV DNA < 400 copies/mL; $^{b}$ At 72 weeks

Keys to Therapeutic Success in HBV

1. Reduce Viral DNA & Antigens
   - Block replication
     - NUCs
     - Capsid inhibitor
     - RNAi
   - Block HBsAg
     - RNAi
     - S-ag Inhibitor
   - Starve cccDNA formation
     - Capsid inhibitor
     - RNAi

2. Reactivate by S-ag reduction
   - RNAi
   - S-ag inhibitor

Activate / Reactivate patient Immune Response
   - PDL-1
   - Interferon
   - STING agonist

‘Functional’ to complete cure
RNAi Mechanism of Action Against HBV

**Effective delivery and siRNA triggers are crucial**

1. **ARB-1467 is a novel antiviral agent in which 3 anti-HBV siRNA “triggers” are packaged inside proprietary lipid nanoparticles (LNPs).**

2. **The 3 siRNA triggers within ARB-1467 are designed to target all 4 viral RNA transcripts encoded by the HBV genome at sites that are highly conserved across HBV genotypes.**

3. **By targeting all 4 viral RNA transcripts, ARB-1467 inhibits production of all HBV viral antigens (Ag), the viral polymerase, HBx protein, and pre-genomic RNA.**

4. **Through knockdown of all HBV viral proteins, it is anticipated that the 3 siRNA triggers within ARB-1467 will inhibit viral replication, remove viral immune suppression and reawaken the immune system.**

5. **ARB-1467 is suitable for use:**
   - Across HBV genotypes
   - Regardless of HBeAg status
   - Regardless of treatment status
   - In combination with currently approved and experimental agents due to complementary MOA, potentially leading to improved outcomes

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*RISC = RNA-Induced Silencing Complex
**pgRNA = pre-genomic RNA*
**ARB-1467 Phase II: Measuring HBsAg Reduction**

### Phase II Study in HBV Patients on Nuc Therapy

- **Duration of Treatment:** 3 months
- **Follow-up:** 12 months after the first dose

#### Cohort 1: HBe-
- **n=8 (6 active, 2 placebo)**
- **0.2 mg/kg monthly**

#### Cohort 2: HBe-
- **n=8 (6 active, 2 placebo)**
- **0.4 mg/kg monthly**

#### Cohort 3: HBe+
- **n=8 (6 active, 2 placebo)**
- **0.4 mg/kg monthly**

#### Cohort 4: HBe-
- **n=12 (12 active)**
- **0.4 mg/kg bi-weekly**

**Up to 1 year extension***

*Detailed results of Cohort 4 will be presented at AASLD*

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*Extension is response guided after first 3 months*
ARB-1467 Multi-Dosing Shows Additive, Stepwise HBsAg Reduction

HBsAg Mean Log (IU/mL) Change from Baseline

*Dosing day
**ARB-1467 Drives Significant HBsAg Reduction**

Reductions of $\geq 1.0 \log_{10}$ in 5/11 patients (after 3 doses at 0.4 mg/kg)

- Potential to achieve greater reductions with continued dosing
- 17/18 patients in Cohorts 1-3 received all three monthly doses

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ARB-1467 (mg/kg)</th>
<th>HBeAg</th>
<th>Multiple Dose HBsAg Reduction ($\log_{10}$ IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>Negative</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>0.4</td>
<td>Negative</td>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>Positive</td>
<td>6</td>
</tr>
<tr>
<td>Placebo</td>
<td>N/A</td>
<td></td>
<td>6&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> The mean serum HBsAg reduction is the nadir value of the arithmetic mean of all values observed at each time point.

<sup>b</sup> Maximum HBsAg reduction is the best single reduction among all patients in a cohort.

<sup>c</sup> Number of patients reaching this threshold

<sup>d</sup> Multiple dose results in Cohort 2 exclude one patient that discounted at day 36 due to “HBV blip” associated with acute HEV infection

<sup>e</sup> Placebo results are based on six subjects (two from each cohort).

**ARBR-1467 was Generally Safe and Well Tolerated**

<table>
<thead>
<tr>
<th>Patients, N (%)</th>
<th>HBeAg-Negative ARB-1467 0.2 mg/kg n=6</th>
<th>HBeAg-Negative ARB-1467 0.4 mg/kg n=6</th>
<th>HBeAg-Positive ARB-1467 0.4 mg/kg n=6</th>
<th>Placebo n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>5 (83)</td>
<td>5 (83)</td>
<td>2 (33)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Grade 3-4 AE</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (17)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>0</td>
<td>1 (17)**</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 or 4 lab abnormalities</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>4 (67)</td>
<td>4 (67)</td>
</tr>
</tbody>
</table>

*Left cochleovestibular deficit, not related to study treatment.

**Subject discontinued treatment after the 2nd dose of ARB-1467 due to “HBV blip” (HBV-DNA 88 IU/ml) –

ALT increase up to 627 U/L on Day 36 of the study associated with HEV super-infection. ALT returned to baseline by Day 60.

• Most AEs were mild and transient. Only two AEs were reported by two subjects; erythema (0.2 mg/kg) and upper respiratory tract infection (placebo). All other AEs were reported by single subjects.
• Isolated elevated glucose, decreased lymphocytes and low phosphate values seen across all treatment groups, including placebo.
• 17/18 (94%) subjects received all three monthly doses.
• No infusion reaction AEs were reported.

Learning from Preclinical Models to Guide Next Steps in Clinic
Preclinical study in infected humanized mouse model with LNP siRNA + pegIFN Combo

- **ARB-1467 & ARB-1740** (RNA interference)
  - Three siRNAs packaged in a lipid nanoparticle delivery system

- **AB-423** (Core/Capsid Inhibitor)
  - Orally administered small molecule
  - Misdirects capsid assembly and inhibits pgRNA encapsidation

- **Pegylated Interferon**
  - Approved drug

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Lee, ACH et al. Exploring Combination Therapy for Curing HBV: Preclinical Studies with Capsid Inhibitor AB-423 and a siRNA Agent, ARB-1740. Presented at AASLD 14 Nov 2016, Boston
Each Agent has Independent Activity Against HBV
siRNA knocks down HBsAg and HBV DNA

Serum HBsAg

Serum HBV DNA

Treatment for 6 weeks

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<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB-423</td>
<td>100 mg/kg</td>
<td>PO</td>
<td>BID</td>
</tr>
<tr>
<td>ETV</td>
<td>1.2 µg/kg</td>
<td>PO</td>
<td>QD</td>
</tr>
<tr>
<td>PegIFN</td>
<td>30 µg/kg</td>
<td>SQ</td>
<td>2×/wk</td>
</tr>
<tr>
<td>ARB-1740</td>
<td>3 mg/kg</td>
<td>IV</td>
<td>biweekly</td>
</tr>
</tbody>
</table>

Lee, ACH et al. Exploring Combination Therapy for Curing HBV: Preclinical Studies with Capsid Inhibitor AB-423 and a siRNA Agent, ARB-1740. Presented at AASLD 14 Nov 2016, Boston
Triple Combo Containing Interferon Shows Better Antigen Control
Preclinical study in infected humanized mouse model

ABA-423 + PegIFN ARB-1740 + ABA-423 + ETV

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<th>Frequency</th>
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<tr>
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HBsAg removal by ARB-1740 correlated with ↑ in human IFN-α expression

Immune response enhanced by addition of IFN to the RNAi combination

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Lee, ACH et al. Exploring Combination Therapy for Curing HBV: Preclinical Studies with Capsid Inhibitor AB-423 and a siRNA Agent, ARB-1740. Presented at AASLD 14 Nov 2016, Boston
ARB-1467 Next Steps to Advance Development

- ARB-1467 is a clinically validated RNA interference agent for the treatment of chronic HBV infection
- ARB-1467 drives significant HBsAg reduction in both eAg-neg and eAg-pos patients
- Longer term ARB-1467 studies with nucs and IFN to begin in 4Q17
- Humanized mouse data support the hypothesis that HBV antigen removal will promote immune recognition and viral control
- Combination of ARB-1467 with approved drugs and/or novel MOA agents can enhance control of HBV and drive progress closer towards cure

ARB-1467 Cohort 4 data in 2H17
Longer term ARB-1467 studies with nucs and IFN to begin in 4Q17
Acknowledgements:
Colleagues and team members at Arbutus, who have together made this progress possible

THANK YOU