Abstract # PS-027

Preclinical antiviral drug combination studies utilizing novel orally bioavailable agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, an HBV RNA destabilizer

Rene Rijnbrand
Arbutus Biopharma Inc.
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Key to Therapeutic Success in HBV

- REDUCE/SUPPRESS VIRAL DNA & ANTIGENS
  - Viral Replication
  - Viral Proteins/HBsAg
  - cccDNA Formation /Function

- RE-AWAKEN/BOOST IMMUNE RESPONSE
  - Reduced HBsAg
  - Immunotherapy

A combination approach to these key factors will drive cures
HBV Lifecycle

Keys to therapeutic success: combining agents with different mechanism of action
HBV Lifecycle

Keys to therapeutic success: combining agents with different MOA
AB-506: A Next Gen HBV Capsid Inhibitor

Potent inhibitor of HBV replication *in vitro*

- Potent inhibition of viral replication in HBV cell culture models ($EC_{50} = 35-80$ nM, $EC_{90} = 200-275$ nM; PHH $EC_{50}$ of 32 nM)
  - Binds at the dimer:dimer interface of core protein
  - Forms capsids devoid of pgRNA
  - Inhibits formation of rcDNA
  - Pan-genotypic activity (HBV genotypes A-H)
  - No cross-resistance with Nuc$^R$ variants
  - High degree of antiviral selectivity for HBV
  - Modest ~6 fold increase in $EC_{50}$ in 40% human serum

- Dose Dependent Reduction in serum HBV DNA in an HDI mouse model of HBV
  - Preclinical data supports potential for QD dosing
  - AB-506 is being advanced into clinical development (mid 2018)
AB-452: A Potent HBV RNA Destabilizer

Novel small molecule HBV RNA Destabilizer

- AB-452 is a potent, highly selective small molecule inhibitor of HBV replication through destabilization of HBV RNA (EC\textsubscript{50} 1.5 nM)

- **In vitro** AB-452 showed:
  - Drop in viral RNA levels
  - Drop in viral s/e/c Ag levels
  - Pan-genotypic activity
  - No cross-resistance with Nuc\textsuperscript{R} variants
  - Highly degree of antiviral selectivity for HBV

- AB-452 significantly inhibited HBV replication and reduced viral RNA and antigens in an immunocompetent AAV mouse model

- AB-452 is being evaluated for advancement into clinical development

Inhibits HBsAg expression in HepG2.2.15 cells with an EC\textsubscript{50} of 1.5 nM

BID PO dosing resulted in up to 1.4 log\textsubscript{10} serum HBsAg reduction. Correlated with liver HBV RNA levels.
ARB-1467
A LNP siRNA agent targeting all HBV transcripts

• Novel RNA interference product
• Unique 3-trigger design inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
• Delivered via proprietary lipid nanoparticle (LNP) technology
• Generally safe and well tolerated to date
• Currently in Phase 2 trials
Combination of AB-506 and AB-452 With NAs and LNP siRNA (ARB-1467)

Molecules are mechanistically compatible
In Vitro Combination Studies: Summary

Molecules are mechanistically compatible

<table>
<thead>
<tr>
<th>HBV Inhibitor</th>
<th>ETV</th>
<th>TDF</th>
<th>TAF</th>
<th>ARB-1467</th>
<th>AB-506</th>
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<tbody>
<tr>
<td>AB-506 Next Gen Capsid Inhibitor*</td>
<td>Additive</td>
<td>Additive</td>
<td>Moderate Synergy</td>
<td>Additive</td>
<td>NA</td>
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<tr>
<td>AB-452 HBV RNA Destabilizer**</td>
<td>sAg</td>
<td>ND</td>
<td>ND</td>
<td>Minor Synergy</td>
<td>ND</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Moderate Synergy</td>
<td>Additive</td>
<td>Additive</td>
<td>ND</td>
<td>Additive</td>
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- *HepDE19 HBV cell culture model with rcDNA quantitation
- **HepG2.2.15 HBV cell culture model with HBV DNA and HBsAg quantitation
**In Vivo Dual and Triple Combination of AB-506, AB-452 and TDF**

HDI Mouse Model of HBV: Serum HBV DNA and HBsAg Reductions

- Dual combinations of AB-506 + AB-452, AB-506 + TDF, and AB-452 + TDF showed strong antiviral activity with mean 1.4, 1.9 and 2.2 log_{10} reductions in serum HBV DNA vs the vehicle control, respectively.
- Triple combination effected larger serum HBV DNA reduction of 2.8 log_{10} vs the vehicle control.
- As expected, serum HBsAg reductions observed only in AB-452 groups.
**In Vivo Dual and Triple Combination of AB-506, AB-452 and TDF**

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Once-Daily Oral Dose × 7 Days
Mean (n=7-8) ± SEM
Open symbol indicates close to LLOQ.

![Graph showing serum HBV DNA reduction](image-url)
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**In vivo Dual and Triple Combination of AB-506, AB-452 and TDF**

HDI Mouse Model of HBV: Liver HBV DNA and HBsAg Reductions

- Liver HBV DNA reductions reflect serum HBV DNA reductions
- AB-506 showed greater effect on liver HBV DNA reduction than TDF
- Only AB-452 containing groups showed liver HBsAg reductions
Summary

• Key to therapeutic success will involve combination of different MoA agents
  • Reduce/Suppress Viral DNA and Antigens
  • Reawaken/Boost host immune responses

• Agents with novel MoA undergoing clinical evaluation; more in preclinical stages
  • eg: Capsid Inhibitors, HBV RNA Destabilizers, RNAi Agents, NA, others

• *In vitro* and *in vivo* antiviral evaluations of Capsid Inhibitor AB-506, RNA Destabilizer AB-452, LNP siRNA ARB-1467 and NA agents show favorable additive to synergistic effects in combination
## Acknowledgments

**Arbutus Team**

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