SB9200: A Novel and Efficacious RIG-I Agonist for Chronic Hepatitis B: Results from cohort 1 of the ACHIEVE Trial

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## Disclosure

<table>
<thead>
<tr>
<th></th>
<th>Gilead Sciences Inc</th>
<th>Arrowhead Research Corp</th>
<th>Spring Bank Pharmaceuticals, Inc.</th>
<th>Roche Molecular</th>
<th>AusBio Ltd</th>
<th>Janssen (J&amp;J)</th>
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<td>Consulting Fees (eg. Advisory Boards)</td>
<td>yes</td>
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<td>Contract Research (grant)</td>
<td>yes</td>
<td>yes</td>
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</table>
The RNA Sensor RIG-I Dually Functions as an Innate Sensor and Direct Antiviral Factor for Hepatitis B Virus

• RIG-I senses the HBV genotype A, B, and C for the induction of type I and III IFNs
• The 5'-ε region of HBV pgRNA is a key element for the RIG-I mediated recognition
• RIG-I counteracts the interaction of HBV polymerase with pgRNA to suppress viral replication
• Type III IFNs are predominantly induced in human hepatocytes during HBV infection

Sato et al., 2015, Cell Immunity 42, 123–132
Inarigivir (SB9200)

- Small molecule nucleic acid hybrid (SMNH)
- Orally bioavailable prodrug
- Active metabolite SB9000
- Actively transported into hepatocytes via OATP1
- 30:1 liver to plasma ratio
- Not metabolized, not phosphorylated.
- Biliary excretion of intact molecule
- No direct activity against DNA polymerase
Aim

• We report here the safety profile as well as molecular virological and serological responses of SB9200-treated patients compared to PL in ACHIEVE Cohort 1 (week 1-24).
20 non-cirrhotic HBV subjects per cohort, randomized 4:1 between SB 9200 and placebo.

12 weeks (SB 9200 monotherapy QD)
- SB 9200- 25 mg
- SB 9200- 50 mg
- SB 9200- 100 mg
- SB 9200- 200 mg
- Placebo

All patients switched to Gilead’s Viread® 300mg monotherapy

12 weeks Viread®

Primary endpoints
- Safety and antiviral activity at 12 weeks

Other Endpoints
- PK, change in serum HBV DNA, HBsAg, HBeAg, HBV RNA and HBcrAg from baseline to weeks 6, 12, 14, 16 and 24
Key Criteria

**Inclusion**
- HBsAg positive for > 6 months
- Treatment naïve for > 6 months
- HBV DNA > 2000 IU/ml for HBeAg –ve and > 20,000 IU/ml for HBeAg +ve
- ALT > ULN but < 150 IU/ml
- FibroScan < 8kPa

**Exclusion**
- F3 or F4 fibrosis
- Evidence of HCC by imaging
- Co-infection with HCV, HIV or HDV
- Creatinine > 1.2mg/dL
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HBeAg- (N=7)</th>
<th>HBeAg+ (N=9)</th>
<th>Placebo (N=4)</th>
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<tbody>
<tr>
<td>ALT</td>
<td>75</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>AST</td>
<td>45</td>
<td>46</td>
<td>46</td>
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<tr>
<td>Bilirubin (umol)</td>
<td>8.6</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Genotype (n)</td>
<td>A-1; B-3; C-1; D-2</td>
<td>B-4; C-5</td>
<td>A-1; B-2; C-1</td>
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<tr>
<td>HBV DNA log_{10} IU/ml</td>
<td>5.69</td>
<td>7.86</td>
<td>6.00</td>
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<tr>
<td>HBsAg log_{10} IU/ml</td>
<td>3.17</td>
<td>4.46</td>
<td>3.70</td>
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</tbody>
</table>

M 12; F8; Asian 18; Cauc 2; Mean Age 40.5 years
1 placebo patient HBeAg positive; 3 HBeAg negative
Mean (+SE) Plasma Concentrations of Sp-SB 9000 and Rp-SB 9000 vs. Time Following Oral Administration of 25 mg SB 9200 – Day 1 vs. Day 42

- No accumulation was observed following multiple once daily dosing of 25 mg SB 9200.
- Half life of metabolite 4 hours
Safety

• No SAE’s
• No AE’s clinical or laboratory grade 3 or greater
• All clinical AE’s mild to moderate
  – > 10%: URTIs, fatigue, headache, GI symptoms
• 3 ALT flares > 200 IU/ml
  – 2 on placebo; 1 on active drug, none > 400 IU/ml
• 3 dose reductions for ALT flare as per protocol
Week 12 HBV DNA reduction on SB9200 or placebo and on switch to TDF from week 12 to 24

Mean HBV DNA (Log10) SB 9200 versus Placebo alone + TDF switch

<table>
<thead>
<tr>
<th>Week</th>
<th>SB 9200 /TDF</th>
<th>Placebo /TDF</th>
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</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>-0.58</td>
<td>+0.33 (p=0.01)</td>
</tr>
<tr>
<td>Week 24</td>
<td>-4.25</td>
<td>-3.39</td>
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</tbody>
</table>

TDF 300mg
Week 12 HBV DNA reduction on SB9200 and on switch to TDF from week 12 to 24

**Individual patient data**

- **Mean HBV DNA HBeAg - SB9200 with TDF switch**
  - Week 12: -0.86
  - Week 24: -3.96
  - TDF 300mg

- **Mean HBV DNA HBeAg + SB 9200 with TDF switch**
  - Week 12: -0.37
  - Week 24: -4.48
  - TDF 300mg

*Patient dose reduced ALT flare*

- HBV DNA reduction significantly greater in HBeAg–ve patients on SB 9200 monotherapy
  - *(p<0.01 versus placebo)*
Week 12 HBsAg reduction on SB9200 and on switch to TDF from week 12 to 24

Individual patient data

Mean HBsAg in HBeAg -ve SB9200 with TDF switch

Mean HBsAg in HBeAg +ve SB 9200 with TDF switch

* Patient dose reduced ALT flare

- ▪ 3 of 16 patients > 0.5 log_{10} sustained reduction in HBsAg at week 12 on monotherapy – all HBeAg –ve
- ▪ 6 of 16 patients > 0.5 log_{10} sustained reduction in HBsAg at week 24 after TDF – 3 HBeAg +ve and 3 HBeAg -ve
Change in HBeAg from baseline

Individual patient data

Change in HBeAg (log10) on SB 9200

Week 12  - 0.16
Week 24  - 0.54

4 of 9 > 0.75 log_{10} at week 24

TDF 300mg

Day 1  Week 2  WK 4  WK 8  WK 12  WK 14  EOS WK 24
Antiviral Activity of SB9200 (Inarigivir) HBV RNA and HBcrAg Profile of ACHIEVE Trial

In HBeAg-NEG group [3 log rapid decline HBV RNA ~1 log gradual decline HBV DNA]

See AASLD Abstract #39 and Late Breaker Poster
Summary: SB9200 Monotherapy (week 0-12)

IN THE HBeAg-NEGATIVE COHORT, HBV RNA AND HBcrAg DECLINE COMPARED TO PLACEBO WERE SIGNIFICANT \([p=0.02 \text{ and } p=0.015 \text{ respectively}]\) (SEE GRAPHS BELOW)

<table>
<thead>
<tr>
<th>Virology Decline</th>
<th>HBeAg-NEG n=7</th>
<th>HBeAg-POS n=9</th>
<th>PL n=4</th>
<th>Rx versus PL</th>
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</thead>
<tbody>
<tr>
<td>HBV DNA ([\geq 1.0 \log_{10} \text{ IU/ml}])</td>
<td>3/7</td>
<td>1/9</td>
<td>0/4</td>
<td>25% vs 0%</td>
</tr>
<tr>
<td>qHBsAg ([\geq 0.5 \log_{10} \text{ IU/ml}])</td>
<td>4/7</td>
<td>1/9</td>
<td>0/4</td>
<td>31% vs 0%</td>
</tr>
<tr>
<td>qHBeAg ([\geq 0.5 \log_{10} \text{ PEIU/ml}])</td>
<td>NA</td>
<td>1/9</td>
<td>0/4</td>
<td>11% vs 0%</td>
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<tr>
<td>HBV RNA ([\geq 3.0 \log_{10} \text{ copies/ml to undetectable}])</td>
<td>3/7</td>
<td>NC</td>
<td>0/4</td>
<td>18% vs 0%</td>
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<tr>
<td>([\geq 1.0 \log_{10} \text{ copies/ml to } &lt; 3 \log_{10} \text{ copies/ml}])</td>
<td>1/7</td>
<td>1/9</td>
<td>0/4</td>
<td>12% vs 0%</td>
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<td>([\geq 0.5 \log_{10} \text{ copies/ml to } &lt; 1 \log_{10} \text{ copies/ml}])</td>
<td>3/7</td>
<td>2/9</td>
<td>1/4</td>
<td>31% vs 25%</td>
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<tr>
<td>HBcrAg ([\geq 1.0 \log_{10} \text{ kU/ml}])</td>
<td>3/7</td>
<td>NC</td>
<td>0/4</td>
<td>18% vs 0%</td>
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<tr>
<td>([\geq 0.5 \log_{10} \text{ kU/ml to } &lt; 1 \log_{10} \text{ kU/ml}])</td>
<td>3/7</td>
<td>1/9</td>
<td>0/4</td>
<td>25% vs 0%</td>
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NA = Not Applicable; NC = No Change; PL = Placebo
SB9200 Partial Responder; TDF responder post SB9200

<table>
<thead>
<tr>
<th></th>
<th>HBV DNA (log10) to D1</th>
<th>HBV RNA (log10) to D1</th>
<th>qHBs (log10) to D1</th>
<th>ALT (log10) to D1</th>
<th>HBcrAg (Log10) to D1</th>
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<td>WK 4</td>
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<td>WK 8</td>
<td>घञ़खञ़</td>
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<td>0.14</td>
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<td>WK 14</td>
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<td>EOS WK 24</td>
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Genotype B
HBeAg - ve

Undetectable
SB9200 Responder and additive effect of TDF

Genotype D
HBeAg - ve

Undetectable
HBV Encapsidation

STOICHEOMETRIC IMBALANCE: One pgRNA; One Polymerase; 240 Core submits

ABSOLUTE REQUIREMENT: 5´-ε pgRNA
Proposed Model for Direct Antiviral Effect of SB9200

HBV Encapsulation: The Packaging Reaction

Conclusion: Clinical

• No safety issues seen at 25mg dose
• PK supports once daily administration and no DDI
• SB9200 25mg low dose monotherapy demonstrates anti-viral efficacy on HBV DNA, HBsAg and HBV RNA at 12 weeks - more prominent in HBeAg –ve patients
• Switch to TDF 300mg from week 12 to week 24 suggestive of enhancement of anti-viral effects including reduction in HBV DNA, HBsAg, HBeAg and HBV RNA
Conclusion: Virology

- SB9200 at a dose of 25mg for 12 weeks resulted in significant antiviral effects on HBV replication.
- Based on the pattern of the key viral biomarkers affected, SB9200 appears to be inhibiting HBV directly at the level of RNA packaging and subsequent reverse-transcription.
- Further studies are warranted.