Imdusiran (AB-729) administered every 8 weeks for 24 weeks followed by the immunotherapeutic VTP-300 maintains lower HBV surface antigen levels in NA-suppressed CHB subjects than 24 weeks of imdusiran alone

Kosh Agarwal¹, Man-Fung Yuen², Stuart Roberts³, Gin-Ho Lo⁴, Chao-Wei Hsu⁵, Wan-Long Chuang⁶, Chi-Yi Chen⁷, Pei-Yuan Su⁸, Sam Galhenage⁹, Sheng-Shun Yang¹⁰, Emily P. Thi¹¹, Katie Anderson¹², Deana Antoniello¹³, Elina Medvedeva¹³, Timothy Eley¹³, Tilly Varughese¹³, Louise Bussey¹², Charlotte Davis¹², Antonella Vardeu¹², Christine L. Espiritu¹¹, Sharie C. Ganchua¹¹, Christina Iott¹¹, Tom Evans¹², Karen D. Sims¹³

¹Institute of Liver Studies, King’s College Hospital, London, United Kingdom, ²The University of Hong Kong, Queen Mary Hospital, Hong Kong, China, ³Alfred Health, Monash University, Melbourne, Australia, ⁴E-Do Hospital, Kaohsiung City, Taiwan, ⁵Chang Gung Memorial Hospital - Lin Kou, Chang Gung University College of Medicine, Taoyuan, Taiwan, ⁶Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, ⁷Chia-Yi Christian Hospital, Ditmanson Medical Foundation, Chiayi City, Taiwan, ⁸Changhua Christian Hospital, Changhua, Taiwan, ⁹Fiona Stanley Hospital, Murdoch, Australia, ¹⁰Taichung Veterans General Hospital, Taichung, Taiwan, ¹¹Arbutus Biopharma, Research, Warminster, PA, United States, ¹²Barinthus Biotherapeutics, Harwell, United Kingdom, ¹³Arbutus Biopharma, Clinical Development, Warminster, PA, United States
Disclosures – Dr. Kosh Agarwal

- Consultancy: Aligos, ASC Therapeutics, Bluejay Therapeutics, DrugFarm, Gilead, GSK, Grifols, Janssen, PrecisionBio, Roche, Surrozen, Tune, Vir

- Grants: Gilead, GSK, Abbott
Current approved therapies for chronic hepatitis B (CHB) slow or prevent the development of HBV-related liver complications, but do not typically lead to functional cure (HBV DNA suppression and HBV surface antigen [HBsAg] loss, with or without HBsAb seroconversion at least 6 months off all treatment)\(^1\)\(^-\)\(^3\)

Excess production of HBsAg is believed to contribute to host immune exhaustion, resulting in inadequate T-cell and B-cell responses to CHB infection and failure to suppress the virus\(^4\)

Therapeutic success will require a combination of agents with complementary mechanisms of action to suppress HBV DNA, reduce HBsAg to low levels, and enhance HBV-specific T-cell responses

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Study Rationale

- Preclinical data in the AAV-HBV mouse model supports lowering HBsAg with an siRNA then following with a therapeutic vaccine to potentiate HBsAg loss and T cell responses\(^1\)

- Imdusiran for 24 weeks (to reduce HBsAg to low levels), followed by VTP-300 (to enhance HBV-specific T cell responses) in NA-suppressed CHB patients may promote HBsAg loss which may lead to functional cure

- **Imdusiran (AB-729/IDR)\(^{2-4}\)**
  - GalNAc-conjugated, single trigger siRNA that blocks all HBV RNA transcripts (including HBx), suppressing viral replication and production of all viral antigens
  - Subcutaneously administered, 60 mg every 8 weeks
  - Lowers mean HBsAg levels by \(~1.5 – 2 \log_{10}\) after 24 – 48 weeks of treatment in combination with NA in multiple studies

- **VTP-300 immunotherapeutic\(^{5-7}\)**
  - 2 viral vectors encoding the same consensus HBV viral sequences used in sequential combination:
    - Chimpanzee adenoviral vector (ChAdOx1-HBV)
    - Modified Vaccinia Ankara vector (MVA-HBV)
  - Generates robust T-cell responses and induces sustained HBsAg declines in a subset of subjects with low HBsAg (<200 IU/mL)
  - Maximal effects on HBsAg reduction observed at least 3 months after dosing

\(^1\)Michler, T. et al. Gastroenterology 2020; 158:1762-1775
\(^2\)Yuen, MF et al. Journal of Hepatology 2022, Volume 77, S876-S877
\(^3\)Yuen, MF et al. 2024 EASL Congress Poster WED-371
\(^4\)MacQuillan, G et al. Hepatology 78(S1):p S1-S2154
\(^5\)Evans, T et al. Journal of Hepatology 2023, Volume 78, S1169-S1170
\(^6\)Sorensen, H et al. Hepatology 2023 78(S1):p S1-S2154
\(^7\)Tak WY et al. Journal of Hepatology 2024, accepted manuscript
Study overview: IM-PROVE II (AB-729-202)

- IM-PROVE II is a randomized, placebo-controlled, multicenter Phase 2a proof-of-concept study (ACTRN12622000317796)
- Primary Objective: To evaluate the safety and reactogenicity of the combination of imdusiran followed by VTP-300 or placebo injection
- Week 48/EOT data is reported for 38/40 subjects who reached timepoint, data to Week 72 and beyond reported as available*

**Study population:**
- NA-suppressed for at least 12 months with HBV DNA < 20 IU/mL
- HBeAg-positive or -negative
- HBsAg ≥100 IU/mL and < 5000 IU/mL
- ALT ≤ 2 × ULN
- Non-cirrhotic

**Protocol decision rules:**
- Optional 2nd MVA-HBV boost/placebo dose at Week 38:
  - Additional ≥0.5 log_{10} HBsAg decline between Weeks 26 and 34
- NA discontinuation occurred after Week 48/EOT visit if all criteria were met:
  - HBV DNA < LLOQ
  - HBeAg negative
  - HBsAg < 100 IU/mL
  - ALT <2 × ULN

*Data cut date April 12, 2024
Demographics: Baseline characteristics were comparable between groups

- Median baseline HBsAg was over 800 IU/mL in each Group
- Mostly male, Asian, with HBV genotype B or C
- More HBeAg+ subjects were randomized to Group B/placebo (not stratified)

### Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A VTP-300 (N=20)</th>
<th>Group B Placebo (N=20)</th>
<th>Total (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>52.2 (6.45)</td>
<td>44.3 (8.33)</td>
<td>48.2 (8.37)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>14 (70)</td>
<td>14 (70)</td>
<td>28 (70.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>18 (90)</td>
<td>19 (95)</td>
<td>37 (92.5)</td>
</tr>
<tr>
<td>White</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>HBV Genotype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5 (25)</td>
<td>7 (35)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>C</td>
<td>7 (35)</td>
<td>7 (35)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>D</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Not detected*</td>
<td>7 (35)</td>
<td>6 (30)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>HBsAg, IU/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>820</td>
<td>870</td>
<td>820</td>
</tr>
<tr>
<td>Mean</td>
<td>1123</td>
<td>1135</td>
<td>1129</td>
</tr>
<tr>
<td>Range</td>
<td>95 - 4000</td>
<td>100 – 3300</td>
<td>95 - 4000</td>
</tr>
<tr>
<td>Baseline ALT mean (SD), U/L</td>
<td>20.7 (9.50)</td>
<td>22.1 (11.12)</td>
<td>21.7 (10.23)</td>
</tr>
</tbody>
</table>

### Assay methods:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Assay Method</th>
<th>Lower Limit of Quantitation</th>
<th>Imputed values for results &lt;LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>DiaSorin Liaison XL</td>
<td>0.05 IU/mL</td>
<td>0.035 IU/mL</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Cepheid Genexpert</td>
<td>10 IU/mL</td>
<td>&lt;LOD: g; TND: 1</td>
</tr>
<tr>
<td>HBeAg</td>
<td>DiaSorin Liaison XL</td>
<td>0.05 PEI IU/mL</td>
<td>0.055 PEI IU/mL</td>
</tr>
<tr>
<td>HBA0</td>
<td>Siemens Centaur</td>
<td>10 mIU/mL</td>
<td>3.5 mIU/mL</td>
</tr>
<tr>
<td>HBV pgRNA</td>
<td>Abbott HCV pgRNA V2.0 (LOD)</td>
<td>0.49 log U/mL</td>
<td>0.48 log U/mL</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Fujirebio Lumiplate G</td>
<td>3 log U/mL</td>
<td>1.45 log U/mL</td>
</tr>
<tr>
<td>HBV GT</td>
<td>DNA/RNA Sequencing</td>
<td>Not amplifiable</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Data cut date

April 12, 2024

*Subjects were NA suppressed at baseline, thus not all had amplifiable DNA or RNA for sequencing*
## Safety: The combination of imdusiran and VTP-300 was well-tolerated

### Subjects, N (%) [Events]

<table>
<thead>
<tr>
<th>Subjects, N (%) [Events]</th>
<th>Imdusiran Lead-in (N=40)</th>
<th>Group A VTP-300 (N=20)</th>
<th>Group B Placebo (N=20)</th>
<th>Study Total (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>22 (55%) [44]</td>
<td>12 (60%) [22]</td>
<td>12 (60%) [24]</td>
<td>30 (75%) [90]</td>
</tr>
<tr>
<td>Grade 1</td>
<td>19 (47.5%) [40]</td>
<td>7 (36.8%) [16]</td>
<td>5 (27.8%) [12]</td>
<td>22 (55.0%) [68]</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (5.0%) [2]</td>
<td>3 (15.8%) [4]</td>
<td>1 (5.6%) [2]</td>
<td>6 (15.0%) [8]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imdusiran VTP-300</td>
<td>4 (10%) [8] N/A</td>
<td>1 (5%) [1]</td>
<td>0</td>
<td>5 (12.5%) [9]</td>
</tr>
<tr>
<td>SAES</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TEAE: treatment-emergent adverse event; SAE: serious adverse event

- Most common treatment-related TEAEs in 2 or more subjects (all Grade 1 or 2):
  - Imdusiran: injection site-related (bruising and/or swelling in 2 subjects), ALT increased in 2 subjects
  - VTP-300: injection site-related (redness, pain and/or injection reaction in 2 subjects)

- Only 3 Grade 3 or 4 laboratory abnormalities were observed, none assessed as AEs:
  - Isolated, transient creatine kinase (CK), glucose, and INR elevations in 3 different subjects

- Well-tolerated profiles of imdusiran and VTP-300 were maintained when administered sequentially
Results: Lower HBsAg levels maintained over time in VTP-300 group

Imdusiran led to declines of $-1.8 \log_{10}$ by Week 26, 95% of subjects had HBsAg <100 at time of VTP-300 or placebo dosing.

More subjects maintained HBsAg thresholds of <100 IU/mL and <10 IU/mL when administered VTP-300 vs placebo.

At 24 weeks post-EOT (Week 72, N=11), there was a significant difference in HBsAg levels between groups, which may reflect the delayed effect of VTP-300 on HBsAg levels observed in other trials.

- BSL = baseline; WK = week; EOT = end of treatment; * 2 subjects did not reach timepoint by data cut; # N=2 and † N=1 subject censored after Week 60 visit due to NA restart.
Results: Individual Subject HBsAg Declines by Treatment Group

More subjects in Group A/VTP-300 have maintained low HBsAg levels at and after end of treatment

- 1 Group A/VTP-300 subject off NA therapy [*] reached HBsAg <LLOQ at Week 72 after >2 log_{10} decline between Week 64 and 72, another subject off NA therapy [#] has had >1.5 log_{10} decline in HBsAg between W60 and W68
- 1 subject in Group B/placebo has had continuous HBsAg <LLOQ for >6 months (remained on NA therapy due to positive HBeAg status at Week 48)
Results: More subjects in Group A/VTP-300 stopped NA treatment

- More subjects in Group A/VTP-300 met NA discontinuation criteria and stopped treatment
  - More Group A/VTP-300 subjects (50%) have maintained HBV DNA <LLOQ off NA therapy than placebo subjects (37.5%)
  - Group A/VTP-300 subjects have maintained lower HBsAg levels after NA discontinuation
    - 1 Group A/VTP-300 subject reached HBsAg <LLOQ at Week 72, another has >1.5 log_{10} HBsAg decline between Week 60 and 68

- NA discontinuation was well-tolerated with frequent follow-up visits and testing of HBV DNA and clinical safety labs
  - Maximal ALT of 80 U/L prior to NA restart amongst 4 subjects who restarted treatment
  - 1 subject had isolated, transient ALT of 156 U/mL after single HBV DNA elevation that spontaneously resolved without re-treatment, subsequently led to HBsAg <LLOQ

### NA Discontinuation Summary

<table>
<thead>
<tr>
<th>N, (%)</th>
<th>Group A VTP-300</th>
<th>Group B placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopped NA treatment after Week 48&lt;sup&gt;8&lt;/sup&gt; (HBV DNA &lt;LLOQ, HBeAg-, ALT &lt;2x ULN, HBsAg &lt;100 IU/mL)</td>
<td>16/19 (84%)</td>
<td>10/19 (53%)</td>
</tr>
<tr>
<td>Did not meet NA stopping criteria: HBeAg+ HBsAg &gt; 100 IU/mL</td>
<td>3/19 (16%) 2/3 1/3</td>
<td>9/19 (47%) 9/9* 3/9*</td>
</tr>
<tr>
<td>Met NA restart criteria&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2/16 (13%)</td>
<td>2/10 (20%)</td>
</tr>
</tbody>
</table>

<sup>8</sup> 2 subjects (1 in each Group) had not reached Week 48 timepoint as of data cut date
<sup>9</sup> 3 subjects were both HBeAg+ and had HBsAg >100 IU/mL
<sup>†</sup> All NA restarts were due to confirmed HBV DNA >20,000 IU/mL without ALT >2x ULN

### Time off of NA therapy

- Group A<sup>‡</sup> (N=14)
  - 36% 36%
- Group B<sup>‡</sup> (N=8)
  - 13% 37%

### HBV DNA <LLOQ most recent visit

- Group A<sup>‡</sup> (N=14)
  - 50% 50%
- Group B<sup>‡</sup> (N=8)
  - 63% 37%

### HBsAg level (IU/mL) at most recent visit

- Group A<sup>‡</sup> (N=14)
  - 14% 29%
- Group B<sup>‡</sup> (N=8)
  - 25% 25%

<sup>‡</sup> only subjects who remained off NA therapy included
Conclusions

- Imdusiran 60 mg every 8 weeks for 24 weeks followed by VTP-300 or placebo was well-tolerated.
- The combination of imdusiran and VTP-300 led to maintenance of lower HBsAg levels during the post-treatment follow-up period.
- Nucleos(t)ide analogue discontinuation was achieved in the majority of subjects, with more meeting the discontinuation criteria in the VTP-300 group (84%) vs placebo (53%).
  - More subjects in the VTP-300 group have maintained HBV DNA < LLOQ and lower HBsAg levels off NA treatment vs placebo.
  - NA discontinuation was well-tolerated, including in the 4 subjects who restarted NA therapy due to HBV DNA increases.
  - No concerning ALT elevations were observed in those subjects.
- Two VTP-300 subjects have had significant (>1.5 log_{10}) HBsAg declines in the early NA discontinuation follow-up period with one subject reaching HBsAg <LLOQ, suggesting a delayed effect of VTP-300 on HBsAg levels as has been previously observed.
Additional imdusiran and VTP-300 data:

- Please see Abstract #2823 (Poster WED-375): Yuen, MF et al., VTP-300 immunotherapeutic, plus low dose PD-1 inhibitor, nivolumab, continues to show meaningful, sustained reductions in HBsAg levels.
- The IM-PROVE II (AB-729-202) low dose nivolumab arm (Group C) is fully enrolled, end of treatment data is expected 2H2024.
Acknowledgements

Arbutus Biopharma and Barinthus Biotherapeutics thank all participating subjects and their families, the Investigators and site staff, Novotech CRO, Eurofins, Maksym Chernyakhovskyy (Arbutus) and Crystal Grant (Arbutus) for data management assistance, Deepa Patel (Arbutus) and Dereck Tait (Barinthus) for study support, and the imdusiran and VTP-300 Research and Development Teams.

Participating Sites:

**UK:**
- Kosh Agarwal, King’s College Hospital, London

**Hong Kong:**
- Man-Fung Yuen, The University of Hong Kong, Queen Mary Hospital

**Australia:**
- Stuart Roberts, Alfred Health, Monash University, Melbourne
- Sam Galhenage, Fiona Stanley Hospital, Murdoch

**Taiwan:**
- Wan-Long Chuang, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung
- Gin-Ho Lo, E-Da Hospital, Kaohsiung City
- Chao-Wei Hsu, Chang Gung Memorial Hospital - Lin Kou, Chang Gung University College of Medicine, Taoyuan
- Chi-Yi Chen, Chia-Yi Christian Hospital, Ditmanson Medical Foundation, Chiayi City
- Pei-Yuan Su, Changhua Christian Hospital, Changhua, Taiwan
- Sheng-Shun Yang, Taichung Veterans General Hospital, Taichung