# Preliminary Safety and Efficacy of the Combination Therapy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) Treating Chronic HBV Infection

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# Disclosure

- Prof. Man Fung Yuen serves as consultant for AbbVie, Aligos Therapeutics, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Bristol Myers Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio Incorporation, GSK, Gilead Sciences, Immunocore, Janssen, Merck Sharp and Dohme, Roche, Silverback Therapeutics, Sysmex Corporation, and Vir Biotechnology
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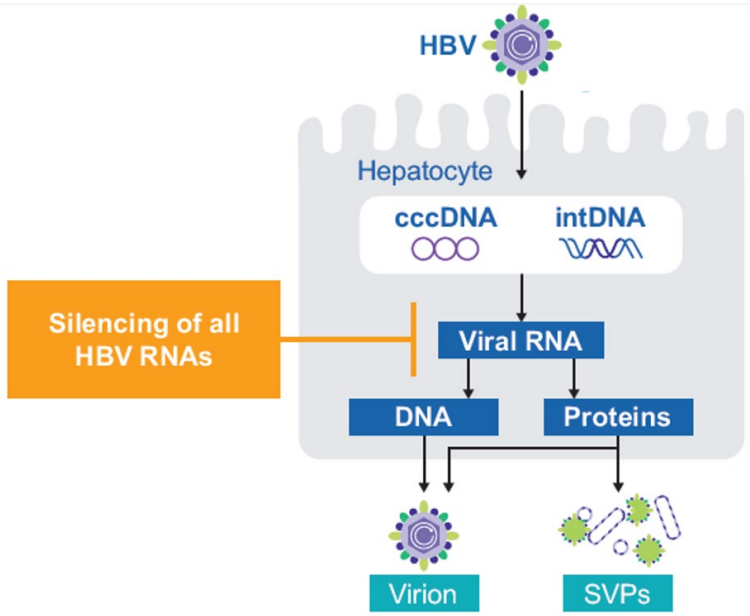
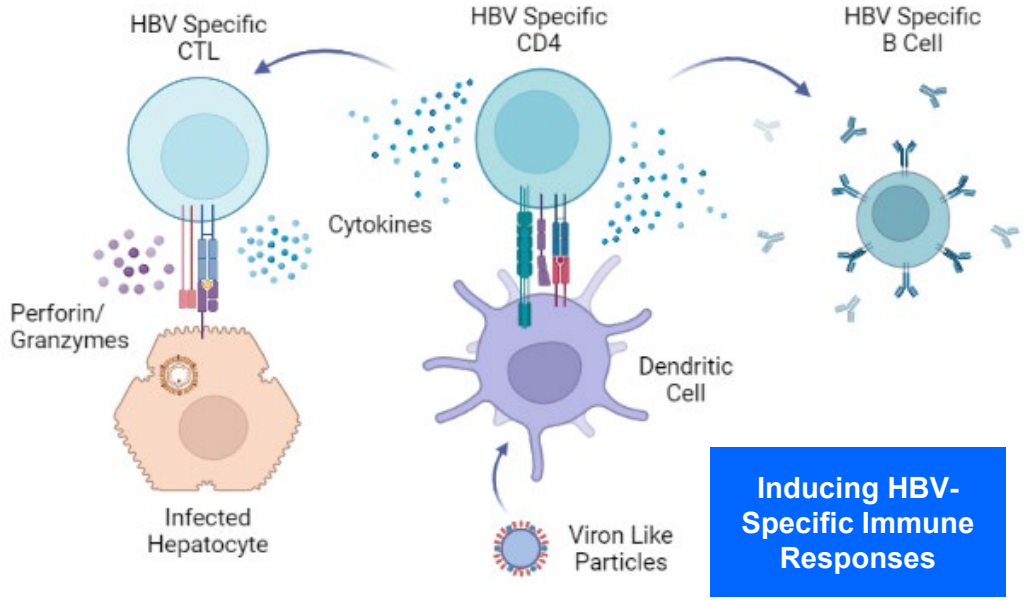
# Combination of BRII-835 and BRII-179 Has the Potential to Regain Immune Control Against Chronic HBV Infection

## Small Interfering RNA
**BRII-835** (VIR-2218)




**GalNAc-conjugated siRNA targeting all HBV viral RNAs blocks viral transcription, reduces viral protein, and alleviates immune suppression**

## Therapeutic Vaccine
**BRII-179** (VBI-2601)



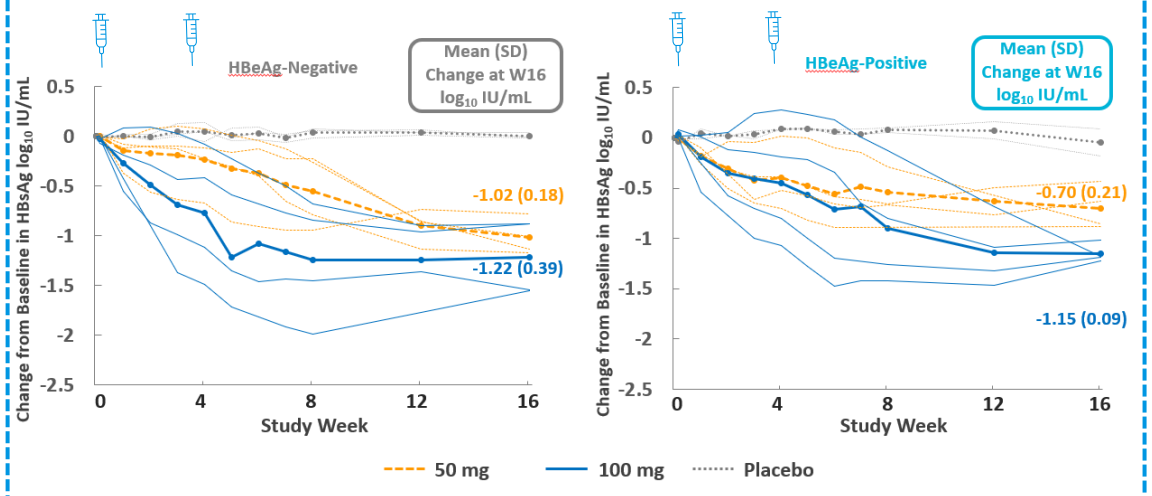

Created with BioRender.com

**Recombinant protein-based vaccine consisting of Pre-S1, Pre-S2, and HBsAg induces HBV-specific B- and T-cell immune responses**

cccDNA, covalently closed circular deoxyribonucleic acid; intDNA, integrated deoxyribonucleic acid; GalNAc, N-Acetylgalactosamine; HBsAg, hepatitis B virus surface protein; siRNA, small interfering ribonucleic acid; SVP, subviral particle

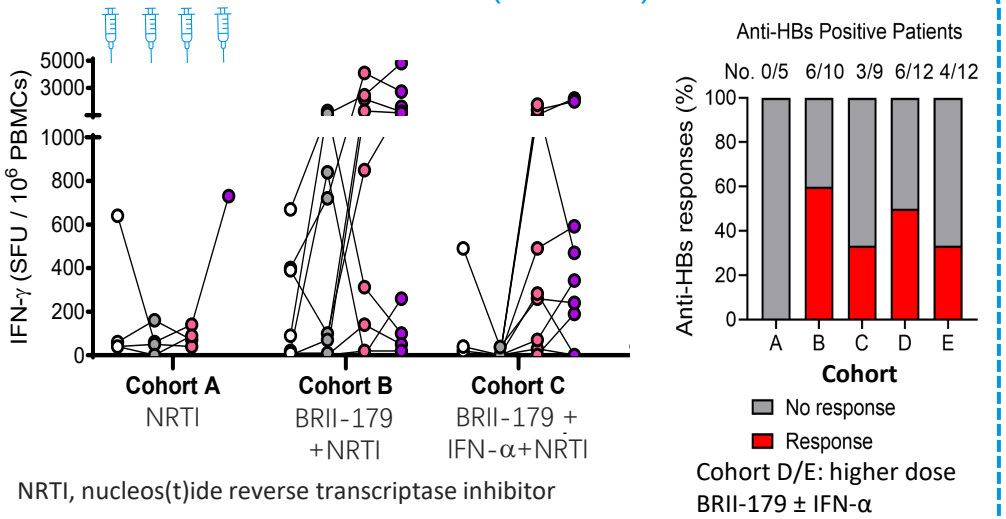
# Proof of Mechanism of BRII-835 and BRII-179 as Single Agents Demonstrated Against Chronic HBV Infection

## Small Interfering RNA
**BRII-835** (VIR-2218)[1]




**Two doses of BRII-835 achieved sustained and dose dependent HBsAg reductions**

## Therapeutic Vaccine
**BRII-179** (VBI-2601)[2,3]




NRTI, nucleos(t)ide reverse transcriptase inhibitor

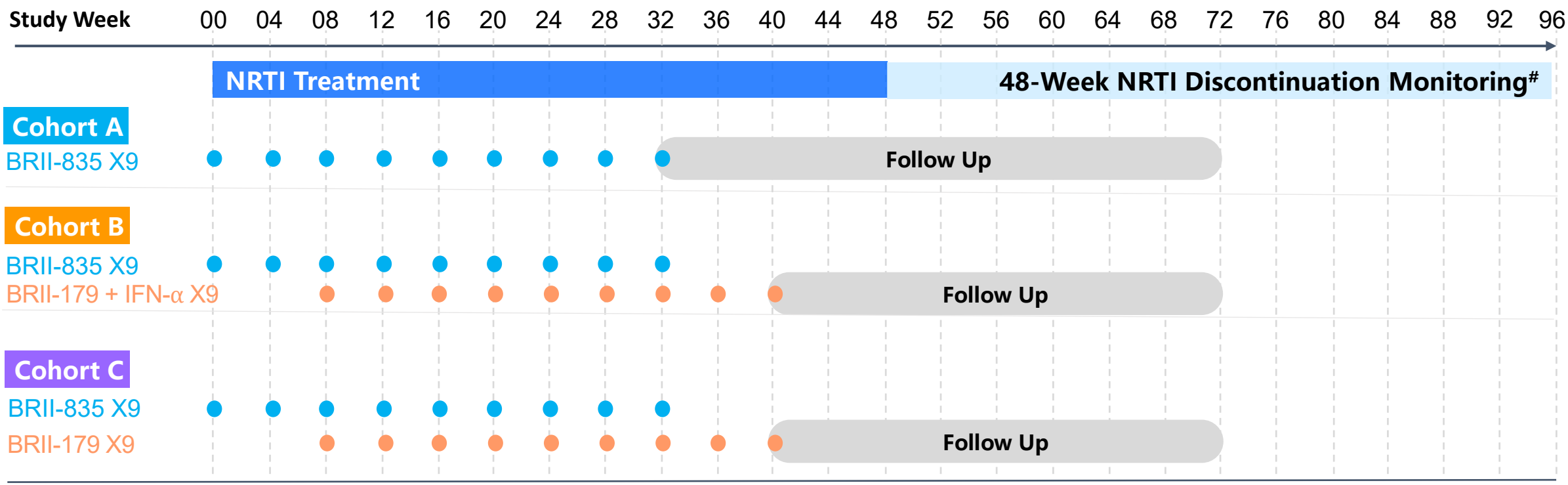
Cohort D/E: higher dose BRII-179 ± IFN-α

**Four doses of BRII-179 induced HBV specific B-cell and T-cell immune responses**

- BRII-835 and BRII-179 were both well tolerated and have good safety profile when administered as single agents
- Notable HBsAg declines were observed with two doses of BRII-835; four doses of BRII-179 induced improved HBV-specific immune responses
- HBsAg seroclearance was not observed with either monotherapy; therefore, the combination treatment of two agents with complementary mechanisms of actions was explored

1. Jia et al. APASL 2022; 2. Ma et al. EASL 2021; 3. Ma et al. JHEP Rep. 2021

# A Phase 2 Trial Evaluating BRII-835 and BRII-179 Combination Therapy




**BRII-835 100 mg via subcutaneous injection (SC) | BRII-179 40 µg ± coadjuvant IFN-α 3 MIU via intramuscular injection (IM)**

# Participants meeting NRTI discontinuation criteria, defined as undetectable HBsAg and HBeAg, alanine aminotransferase < 2x upper limit of normal, and HBV DNA < LLOQ, will be eligible to withdraw NRTI therapy

- Adult participants on NRTI ≥ 12 months with HBV DNA < LLOQ were enrolled
- Preliminary safety and efficacy data through Week 40 are presented

IFN-α, interferon-alpha; LLOQ, lower limit of quantitation; NRTI, nucleos(t)ide reverse transcriptase inhibitor

# Demographics and Baseline Characteristics Were Generally Balanced

| | Cohort A (N = 11*) | Cohort B (N = 20) | Cohort C (N = 20) |
|---|---|---|---|
| **Mean Age ± SD (years)** | 45.9 ± 10.5 | 47.6 ± 9.1 | 45.3 ± 9.5 |
| **Male, n (%)** | 8 (72.7%) | 14 (70.0%) | 15 (75.0%) |
| **Race, n (%)** | | | |
| Asian | 11 (100%) | 18 (90.0%) | 18 (90.0%) |
| Black or African American | 0 | 2 (10.0%) | 1 (5.0%) |
| White | 0 | 0 | 1 (5.0%) |
| **HBeAg Status at Baseline, n (%)** | | | |
| Negative | 9 (81.8%) | 15 (75.0%) | 14 (70.0%) |
| Positive | 2 (18.2%) | 5 (25.0%) | 6 (30.0%) |
| **Median (Range) Baseline HBsAg (IU/mL)** | 387.3 (145.4, 1222.0) | 694.7 (175.8, 6479.0) | 832.7 (160.2, 3169.0) |
| **Mean Baseline $\log_{10}$ HBsAg ± SD (IU/mL)** | 2.63 ± 0.30 | 2.97 ± 0.42 | 2.90 ± 0.35 |
| **Mean Baseline ALT ± SD (U/L)** | 20.3 ± 11.4 | 21.4 ± 9.5 | 21.6 ± 9.9 |

* One participant withdrew consent prior to study drug administration

ALT, alanine aminotransferase; HBeAg, hepatitis B virus e antigen; HBsAg, hepatitis B virus surface antigen; SD, standard deviation

- Baseline HBsAg was lower in Cohort A compared with Cohort B or C

# BRII-835 Alone or in Combination with BRII-179 ± Coadjuvant IFN-α Were Well Tolerated

| | Cohort A (N = 10) | Cohort B (N = 20) | Cohort C (N = 20) |
|---|---|---|---|
| **Any TEAEs** | 10 (100%) | 19 (95.0%) | 20 (100%) |
| **Grade 1 TEAEs** | 10 (100%) | 19 (95.0%) | 17 (85.0%) |
| **Grade 2 TEAEs** | 1 (10.0%) | 7 (35.0%) | 6 (30.0%) |
| **≥ Grade 3 TEAEs** | 0 | 0 | 2 (10.0%) |
| **BRII-835 Related TEAEs** | 7 (70.0%) | 13 (65.0%) | 10 (50.0%) |
| **BRII-179 + IFN-α Related TEAEs** | NA | 17 (85.0%) | NA |
| **BRII-179 Related TEAEs** | NA | NA | 10 (50.0%) |
| **Serious TEAEs*** | 0 | 1 (5.0%) | 3 (15.0%) |
| **AEs Leading to Treatment Discontinuation#** | 0 | 0 | 1 (5.0%) |
| **AEs Leading to Study Discontinuation#** | 0 | 0 | 1 (5.0%) |

NA, not applicable; TEAE, treatment-emergent adverse event

*One chest pain (non-cardiac) in Cohort B; one each of duodenal ulcer, Ludwig's angina, and chest pain (non-cardiac) in Cohort C

# One participant experiencing duodenal ulcer withdrew study prematurely

- Majority of TEAEs was grade 1 or 2 in severity; none of ≥ grade 3 or serious TEAEs were treatment related
- Most common TEAEs across cohorts were injection site reactions (56.0%)
- TEAEs with higher incidence in Cohort B (i.e., headache, fatigue, myalgia, and pyrexia) were consistent with the known side effects of IFN-α

# BRII-835 Alone or in Combination with BRII-179 ± Coadjuvant IFN-α Were Well Tolerated

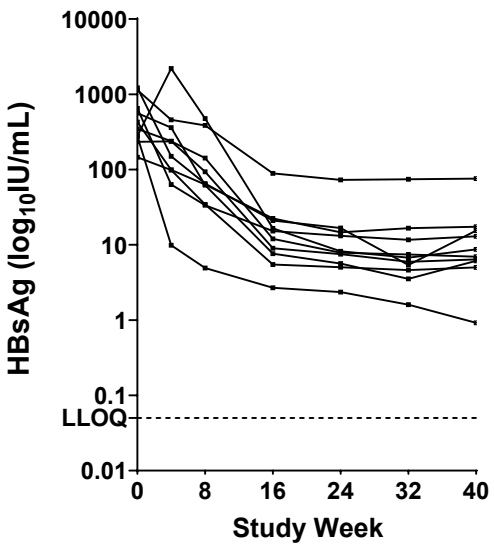
| | Cohort A (N = 10) | Cohort B (N = 20) | Cohort C (N = 20) |
|---|---|---|---|
| **ALT Increased** | | | |
| Grade 1 | 5 (50.0%) | 6 (30.0%) | 10 (50.0%) |
| Grade 2 | 0 | 0 | 0 |
| ≥ Grade 3 | 0 | 0 | 0 |
| **AST Increased** | | | |
| Grade 1 | 3 (30.0%) | 7 (35.0%) | 6 (30.0%) |
| Grade 2 | 0 | 1 (5.0%) | 0 |
| ≥ Grade 3 | 0 | 0 | 0 |
| **Total Bilirubin Increased** | | | |
| Grade 1 | 0 | 2 (10.0%) | 0 |
| Grade 2 | 0 | 0 | 0 |
| ≥ Grade 3 | 0 | 0 | 0 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase

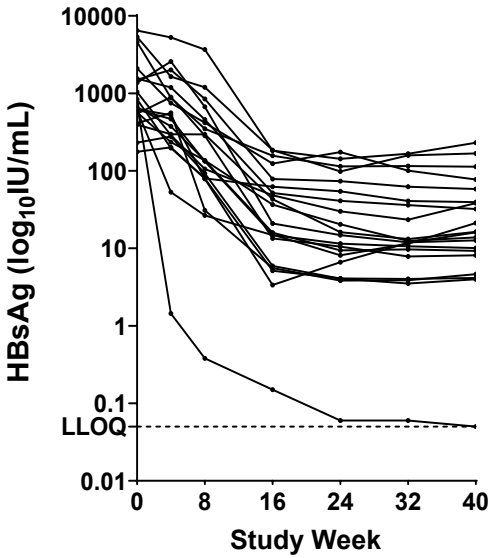
- Mild asymptomatic ALT and/or AST elevations were observed; mostly grade 1 in severity
- Two participants experienced borderline total bilirubin elevations (22 and 23 µmol/L, respectively); none were reported as an AE

# Notable HBsAg Reductions Observed with BRII-835 Alone or in Combination with BRII-179 ± Coadjuvant IFN-α

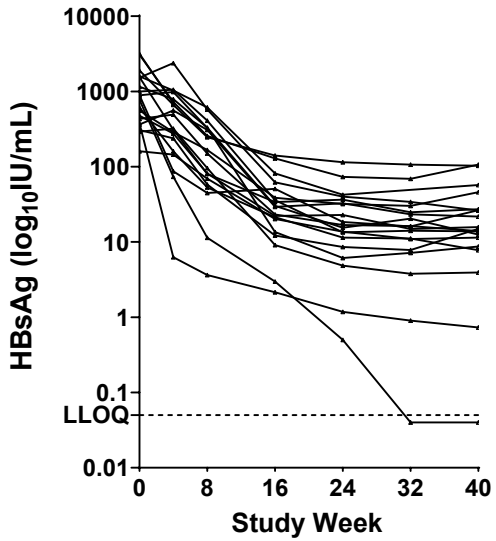
**Cohort A**
BRII-835 Q4W X9




**Cohort B**
BRII-835 Q4W X9
BRII-179 + IFN-α Q4W X9




**Cohort C**
BRII-835 Q4W X9
BRII-179 Q4W X9



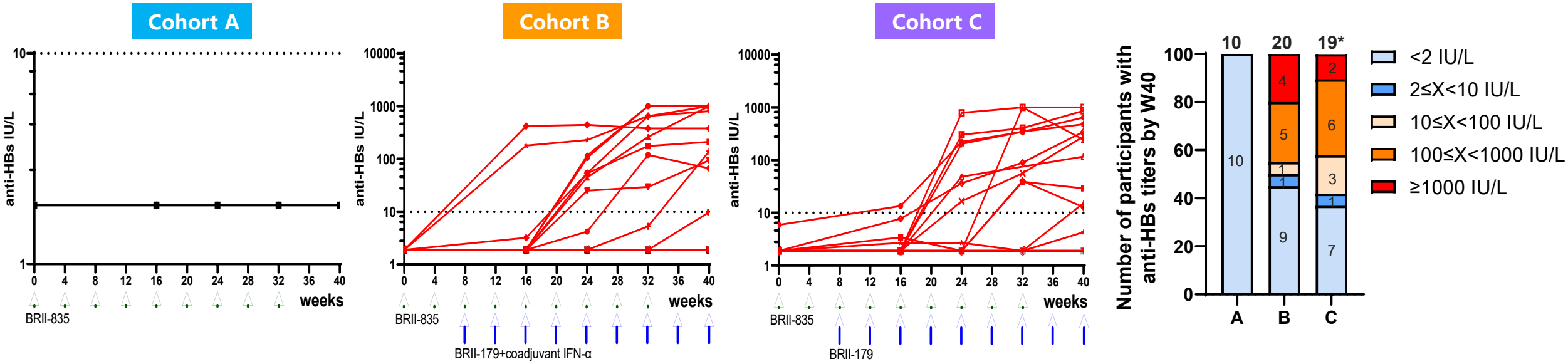

**Mean (SD) Change from Baseline ($log_{10}$ IU/mL)**

| | Week 32 (siRNA EOT) | Week 40 (Combo EOT) |
|---|---|---|
| Cohort A (N=10) | -1.75 (0.39) | |
| Cohort B (N=20) | -1.78 (0.58) | -1.75 (0.60) |
| Cohort C (N=20) | -1.81 (0.71) | -1.77 (0.72) |

- Mean HBsAg reductions from baseline were comparable across cohorts
- Two participants (Cohorts B & C) achieving HBsAg ≤ LLOQ (0.05 IU/mL) by Week 40 received combination treatment

LLOQ, lower limit of quantitation

# BRII-179 in Combination with BRII-835 Induced Stronger Anti-HBs Response



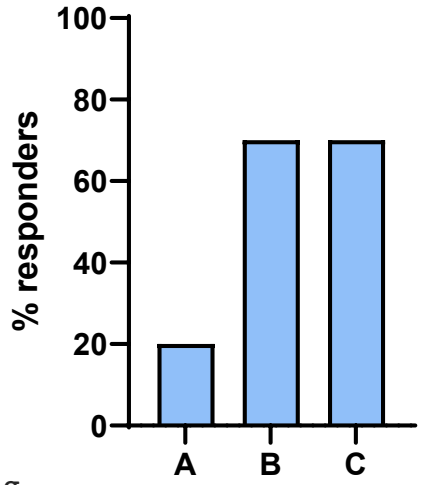

- BRII-179 induced potent anti-HBs response, generally peaking after 5 doses with titers reaching the upper limit of the assay at 1000 IU/L
- ≥ 40% of participants in Cohorts B and C mounted high anti-HBs titers (> 100 IU/L) by Week 40
- Two early responders with antibody titer peaking after two injections of BRII-179 were only observed in BRII-179 + coadjuvant IFN-α group
- Combination treatment of BRII-179+BRII-835 resulted in a higher percentage of participants with anti-HBs levels above 100 IU/L (44%) compared to BRII-179 monotherapy (4 doses, 17%) (Ma et al. *JHEP Rep.* 2021)

* One participant withdrew from study prior to Week 8 and did not have available post baseline anti-HBs data

# BRII-179 in Combination with BRII-835 Led to Improved HBV Surface-Antigen-Specific T-Cell Response in Evaluable Participants

**IFN-γ ELISpot Peak Sum SFU through Week 44 > 3-fold compared to baseline* in evaluable participants#**

| | Cohort A | Cohort B | Cohort C |
|---|---|---|---|
| ***In vitro* (peptide pools)** | 1/5 (20%) | 7/10 (70%) | 7/10 (70%) |




*SFU: spot forming unit of IFN-γ releasing HBsAg-/PreS1-/PreS2-specific T cells
Baseline defined as the maximum of pre-treatment SFU
#Available data from the first 25 evaluable participants are presented. Analysis of the remaining samples is ongoing

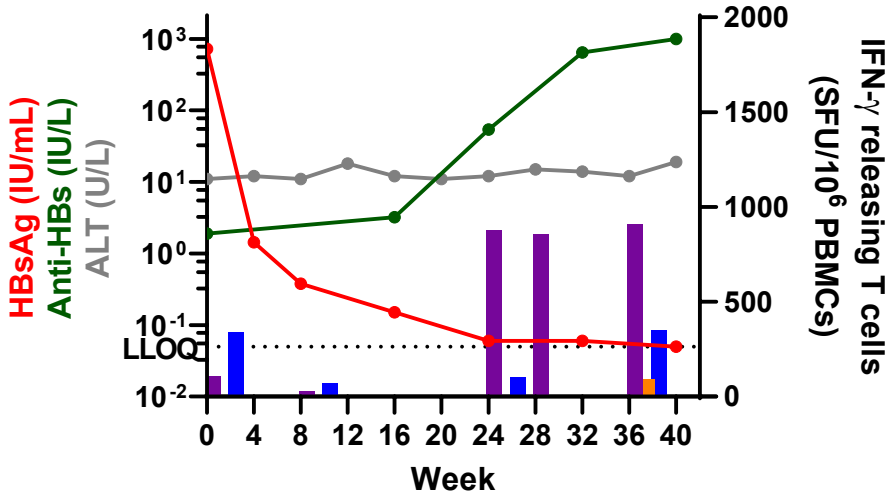
- BRII-835 alone may restore HBV surface-antigen-specific T-cell responses in a small subset of participants
- BRII-179 with or without coadjuvant IFN-α induced improved HBV surface-antigen-specific T-cell responses in combination with BRII-835
- Comparable HBV surface-antigen-specific T-cell responses were observed in the two combination cohorts receiving BRII-835 and BRII-179 with or without coadjuvant IFN-α
- Combination treatment of BRII-179+BRII-835 resulted in a higher proportion of participants with greater magnitude of T cell responses (>20-fold of baseline) compared to BRII-179 monotherapy (40% vs 25%) (Ma et al. *JHEP Rep.* 2021)

# Robust Anti-HBs and T-Cell Response Observed in Two Participants Achieving HBsAg ≤ LLOQ

## Cohort B

**Subject 1**

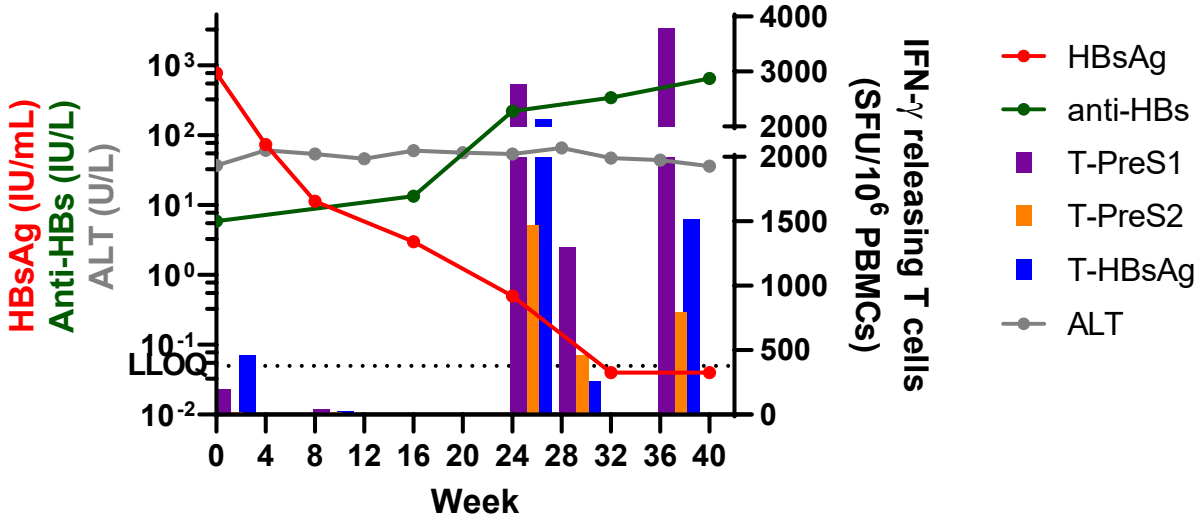
(baseline HBsAg 723 IU/mL)




## Cohort C

**Subject 2**

(baseline HBsAg 776 IU/mL)




- One participant in Cohort C achieved HBsAg loss and seroconversion at Week 32; one participant in Cohort B achieved HBsAg at LLOQ (0.05 IU/mL) at Week 40
- Both participants achieved HBsAg reduction from baseline > 4 $\log_{10}$ with robust anti-HBs and T-cell responses
- Testing correlation between anti-HBs and T-cell responses and overall HBsAg response remains ongoing

LLOQ, lower limit of quantitation

# Conclusions

- Treatment of BRII-835 (siRNA) alone or in combination with BRII-179 (therapeutic vaccine) ± coadjuvant IFN-α was well tolerated. No significant difference in mean HBsAg reductions among all cohorts at the end of treatment

- BRII-179 in combination with BRII-835 induced potent anti-HBs responses (>100 IU/L) in ≥ 40% of participants compared to 0% in BRII-835 alone cohort. The combination regimens also led to improved HBV surface-antigen-specific T-cell responses compared to BRII-835 alone (70% vs. 20%)

- Overall improved antibody and HBV-specific T-cell responses were observed with combination treatment of BRII-835 and BRII-179 compared to BRII-179 monotherapy

- Two participants who achieved HBsAg ≤ LLOQ had robust anti-HBs and T-cell responses with maximum HBsAg reduction of > 4 $\log_{10}$. Follow-up for longer-term responses and immune correlation is ongoing

- Optimization of the combination regimens is underway to further enhance immune responses and achieve a higher rate of functional cure

# Acknowledgement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