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Breakthrough innovation & insight

# Safety and Antiviral Activity of Two Monthly Administration of BRII-835 (VIR-2218), an X-Targeting RNAi Therapeutic, in Chinese Patients with Chronic HBV Infection

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# Disclosure

- Advisory service to Gilead, GSK, and J&J

# Introduction

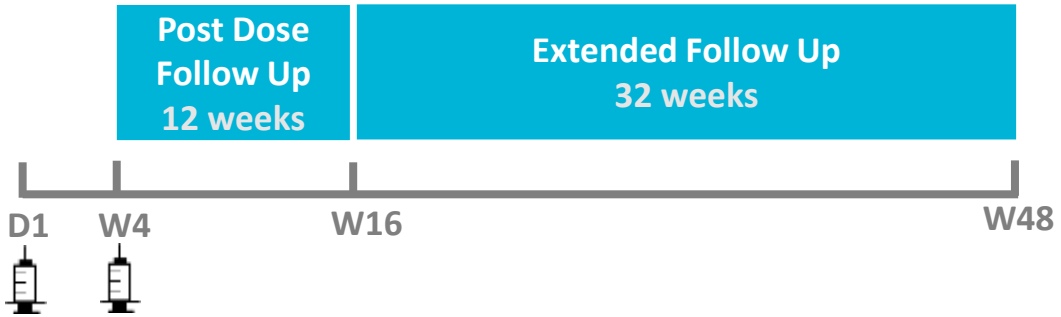
- **BRII-835 (VIR-2218) is an investigational GalNAc-conjugated small interfering RNA (siRNA) therapeutic targeting a specific region within *HBX* which is shared by all HBV viral transcripts**
- **A previous study in CHB patients in Asia Pacific Region showed[1]**
  - ✓**Two doses of VIR-2218 at 20-200 mg given monthly were well tolerated**
  - ✓**Dose-dependent reductions in HBsAg in both HBeAg- and HBeAg+ subjects across all dose levels**
- **Safety, tolerability, and antiviral activity from a phase 2 randomized, double-blind, placebo-controlled trial of BRII-835 in Chinese patients with CHB is presented**

[1] Gane E, et al. EASL 2021. #OS-44

# Study Design

- **Adults with non-cirrhotic HBeAg- or HBeAg+ CHB on NRTI therapy were randomized (4:1) to receive two doses of BRII-835 or placebo via SC injections 4 weeks apart**
- **Subjects achieving serum HBsAg decrease from baseline > 1 $log_{10}$ by Week 16 were followed up to Week 48**

| | | |
|---|---|---|
| **HBeAg-Negative CHB** | **50 mg SC n = 5** | **100 mg SC n = 6*** |
| **HBeAg-Positive CHB** | **50 mg SC n = 5** | **100 mg SC n = 5** |




* Number of planned subjects was 5. One additional subject was enrolled and randomized to placebo group.

NRTI, nucleos(t)ide reverse transcriptase inhibitors

# Key Inclusion/Exclusion Criteria

## Inclusion

- Aged 18 to 65 years
- HBsAg+ ≥ 6 months
- On NRTI therapy ≥ 6 months
- HBsAg > 150 IU/mL
- HBV DNA < 90 IU/mL
- ALT and AST ≤ 2x ULN

## Exclusion

- Significant fibrosis or cirrhosis, defined as Fibroscan > 8.5 kPa at screening or a liver biopsy within 1 year showing Metavir F3/F4
- Bilirubin > ULN or INR > 1.1x ULN
- Active infection with HIV, HCV, or HDV
- Creatinine clearance < 60 mL/min (Cockcroft-Gault formula)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NRTI, nucleos(t)ide reverse transcriptase inhibitors; ULN, upper limit of normal

# Demographics and Baseline Characteristics

| | HBeAg-Negative | | | HBeAg-Positive | | | |
|---|---|---|---|---|---|---|---|
| | BRII-835 | | Placebo N = 3 | BRII-835 | | Placebo N = 2 | Overall N = 21 |
| | 50 mg N = 4 | 100 mg N = 4 | | 50 mg N = 4 | 100 mg N = 4 | | |
| Mean Age (± SD), years | 48.5 (9.7) | 36.5 (9.3) | 31.0 (5.2) | 41.8 (4.3) | 39.5 (10.7) | 38.0 (11.3) | 39.7 (9.3) |
| Male, n (%) | 4 (100.0) | 4 (100.0) | 3 (100.0) | 3 (75.0) | 3 (75.0) | 1 (50.0) | 18 (85.7) |
| Mean BMI (± SD), $kg/m^2$ | 24.5 (1.6) | 24.1 (1.7) | 24.2 (2.6) | 26.9 (2.8) | 24.6 (3.0) | 21.3 (0.1) | 24.5 (2.5) |
| Mean $log_{10}$ HBsAg (± SD), IU/mL | 2.82 (0.49) | 3.28 (0.79) | 2.95 (0.48) | 3.60 (0.55) | 3.24 (0.49) | 3.72 (0.07) | 3.24 (0.58) |
| Mean ALT (± SD), U/L | 24.5 (4.5) | 21.3 (8.9) | 15.0 (4.4) | 15.5 (9.2) | 17.0 (9.1) | 16.0 (1.4) | 18.6 (7.4) |

SD, standard deviation; ALT, alanine aminotransferase
Upper limit of normal of ALT: 41 U/L (male), 37 U/L (female)

# Overall Safety and Tolerability

| Number of Subjects (%) | HBeAg-Negative | | | | HBeAg-Positive | | | |
|---|---|---|---|---|---|---|---|---|
| | BRII-835 | | | Placebo N = 3 | BRII-835 | | | Placebo N = 2 |
| | 50 mg N = 4 | 100 mg N = 4 | Overall N = 8 | | 50 mg N = 4 | 100 mg N = 4 | Overall N = 8 | |
| Any TEAEs | 1 (25.0) | 2 (50.0) | 3 (37.5) | 0 | 2 (50.0) | 1 (25.0) | 3 (37.5) | 1 (50.0) |
| Grade 1 TEAEs | 0 | 1 (25.0) | 1 (12.5) | 0 | 2 (50.0) | 1 (25.0) | 3 (37.5) | 1 (50.0) |
| Grade 2 TEAEs | 1 (25.0) | 1 (25.0) | 2 (25.0) | 0 | 0 | 0 | 0 | 0 |
| Grade ≥ 3 TEAEs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug-Related TEAEs | 0 | 0 | 0 | 0 | 1 (25.0) | 1 (25.0) | 2 (25.0) | 0 |
| Serious TEAEs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TEAEs Leading to Study Discontinuation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

TEAE, treatment-emergent adverse event

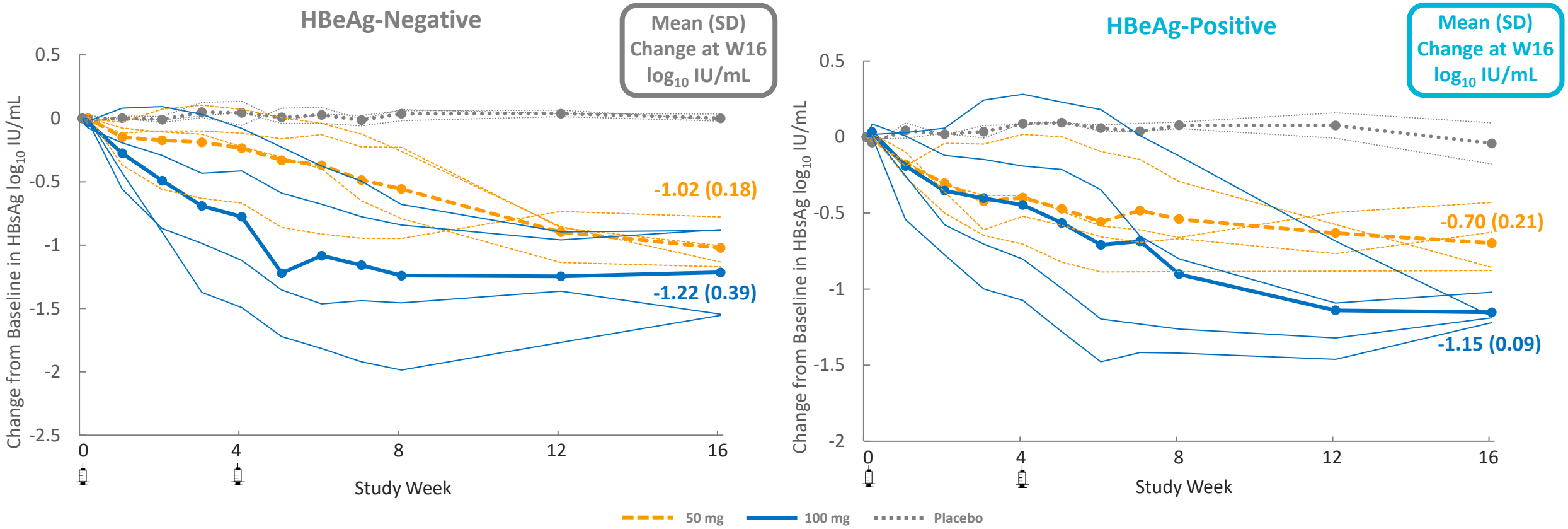
- No dose dependent patterns observed in the incidence of TEAE
- All AE terms were reported in no more than 1 subjects receiving BRII-835 or placebo
- All drug-related TEAEs were grade 1 [diarrhea, epigastric discomfort, fatigue, decreased appetite, and somnolence]

# Liver Function Monitoring

| | HBeAg-Negative | | | | HBeAg-Positive | | | |
|---|---|---|---|---|---|---|---|---|
| | BRII-835 | | | Placebo N = 3 | BRII-835 | | | Placebo N = 2 |
| | 50 mg N = 4 | 100 mg N = 4 | Overall N = 8 | | 50 mg N = 4 | 100 mg N = 4 | Overall N = 8 | |
| Grade 1 ALT Increased | 0 | 2 (50.0) | 2 (25.0) | 0 | 1 (25.0) | 2 (50.0) | 3 (37.5) | 0 |
| Grade 1 AST Increased | 1 (25.0) | 0 | 1 (12.5) | 0 | 0 | 2 (50.0) | 2 (50.0) | 0 |
| Grade 1 Total Bilirubin Increased | 1 (25.0) | 1 (25.0) | 2 (25.0) | 1 (33.3) | 0 | 1 (25.0) | 1 (12.5) | 1 (50.0) |

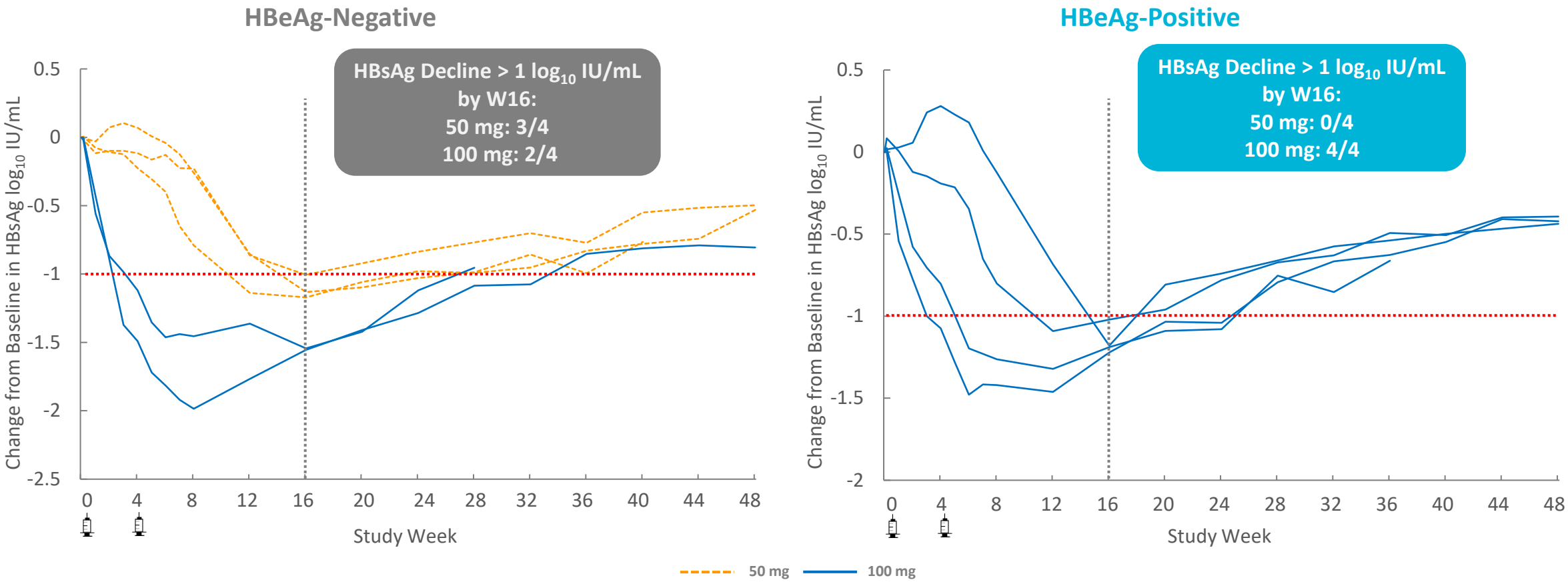
- ALT and AST elevations were 1-2x ULN.
- Total bilirubin elevations not exceeding 1.5x ULN
- No ALT and/or AST elevations were concurrent with bilirubin increases

# Serum HBsAg Change from Baseline Through Week 16



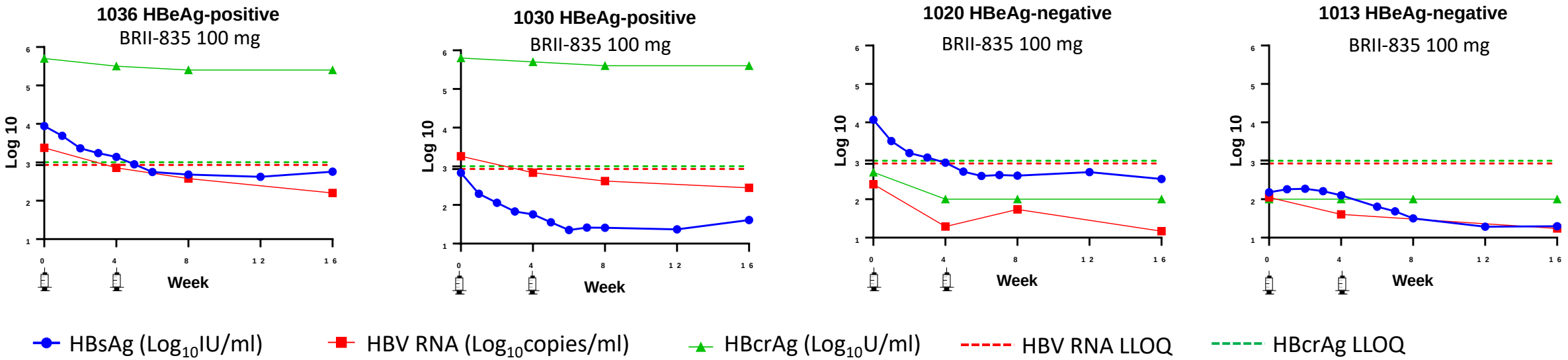

- **Consistently greater decline from baseline in serum HBsAg achieved in both HBeAg- and HBeAg+ subjects receiving BRII-835 than placebo**
- **Greater HBsAg reductions observed in the 100 mg cohort than in the 50 mg cohort**

# HBsAg Kinetics Through Week 48 in Extended Follow Up




- **6/8 subjects receiving BRII-835 100 mg achieved HBsAg decline > 1 $log_{10}$ by Week 16**
- **Serum HBsAg in all subjects entering extended follow-up remained below baseline through Week 48**

# Change of Exploratory Viral Markers for Individual Subjects




- **Baseline HBV RNA and HBcrAg levels were < LLOQ in evaluable HBeAg-negative subjects*, suggesting a proportion of HBsAg may be derived from integrated HBV DNA**
- **Of the evaluable subjects with data*, notable HBsAg reductions were observed in HBeAg-negative and HBeAg-positive subjects, suggesting that BRII-835 may target HBsAg transcripts derived from both cccDNA and integrated HBV DNA**

*Evaluable subjects included 2 HBeAg-negative and 4 HBeAg-positive subjects with available baseline markers. Baseline HBV RNA and HBcrAg were > LLOQ for all HBeAg-positive subjects, but < LLOQ in HBeAg-negative subjects

# Conclusions

- Two monthly doses of BRII-835 administered SC were well tolerated in Chinese patients with non-cirrhotic chronic HBV infection
- Dose-dependent reductions from baseline in serum HBsAg levels were achieved through 12 weeks post last dose in both HBeAg-negative and HBeAg-positive subjects
- In all subjects achieving HBsAg decline > 1 $\log_{10}$ IU/mL at Week 16 (12 weeks post last dose), serum HBsAg remained below baseline through Week 48
- The data supports further development of BRII-835 as a key component of combination regimens to achieve functional cure for chronic HBV infection

# Acknowledgement


- **We thank all participating subjects and their families, the investigators and site staff, IQVIA, Q2 Solutions, Wuxi AppTec, Vir Biotechnology, and BRII-835 Research and Development Teams.**