Restoration of HBV-specific immune responses with therapeutic vaccine BRII-179 (VBI-2601) in chronic HBV patients in a phase 1b/2a study

Haiyan Ma[1], Tien Huey Lim[2], Apinya Leerapun[3], Martin Weltman[4], Jidong Jia[5], Young-Suk Lim[6], Pisit Tangkijvanich[7], Wattana Sukeepaisarnjaroen[8], Yun Ji[9], Nina Le Bert[1], Dong Li[10], Yao Zhang[10], Robert Hamatake[9], Nicole Tan[1], Chunming Li[10], Simone I Strasser[11], Huiguo Ding[12], Jung-Hwan Yoon[13], Nigel Stace[14], Tanvir Ahmed[15], Dave Anderson[15], Li Yan[9], Antonio Bertoletti[1], Qing Zhu[9], **Man-Fung Yuen[16]**

[1]Programme in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore, [2]Middlemore Hospital, Auckland, New Zealand; [3]Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand; [4]Nepean Hospital, Kingswood, Australia; [5]Beijing Friendship Hospital, Beijing, China; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [7]Center of Excellence in Hepatitis and Liver Cancer, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [8]Srinagarind Hospital, Khon Kaen, Thailand; [9]Brii Biosciences Inc. Durham, NC, USA; [10]Brii Biosciences Inc. Beijing, P.R.China; [11]Royal Prince Alfred Hospital, Camperdown, Australia; [12]Beijing You 'an Hospital affiliated to Capital Medical University, Beijing, China; [13]Seoul National University Hospital, Seoul, South Korea; [14]Capital & Coast District Health Board, Wellington, New Zealand; [15]VBI Vaccines, Cambridge, MA, USA; [16]The University of Hong Kong, Queen Mary Hospital, Hong Kong

INTRODUCTION

Functional cure of chronic hepatitis B virus (HBV) infection without life-long treatment requires a restoration of defective HBV-specific humoral and cellular immunity. Therapeutic vaccines based on the major structural and non-structural proteins have been tested in chronic HBV (CHB) patients but have shown scarce immunogenicity. BRII-179, also known as VBI-2601, a novel formulation comprised of all three HBV surface envelope proteins (Pre-S1, Pre-S2, and S), induced Th1-skewed humoral and cellular responses in preclinical naïve or HBV-AAV mouse models [1, 2].

AIM

To evaluate the safety, antiviral activity, and immunogenicity of BRII-179 (VBI-2601) with or without admixing co-adjuvant IFN-α in CHB patients.

METHOD

- BRII-179-001 study was a randomized, open-label, controlled phase 1b/2a study included two dose levels of BRII-179 (VBI-2601) at 20 μg (Part 1) and 40 μg (Part 2) (**Table 1**).
- In cohorts A to E, HBeAg positive or negative, Nrtl-experienced CHB patients were enrolled and received 4 monthly intramuscular injections of BRII-179 (VBI-2601) admixed with/without 3 MIU IFN-α (**Table 1**).
- All patients continued with daily Nrtl treatment on Day 1 and continued beyond the end of dosing of BRII-179 (VBI-2601).
- Study visits were at screening and on Days 1, 28, 56, 84, then extended follow up for 3 months on Days 112, 140, and 168.
- Safety evaluation included clinical laboratory and adverse events (AEs) assessments. Antibody and cellular responses to hepatitis B surface antigens, as well as quantification of circulating HBsAg were monitored.

Table 1: Study design

Part	Cohort	N	CHB HBeAg pos/neg (cont'd Nrtl therapy)
1	A	5*	control (Nrtl only)
	B	10	4 x 20μg Q4W
	C	10	4 x 20μg + IFN-α Q4W
2	D	12	4 x 40μg Q4W
	E	12	4 x 40μg + IFN-α Q4W

CHB: Chronic Hepatitis B; Cont'd: continued treatment; pos.: positive; neg: negative; Q4W: every 4 weeks; NA: not applicable; Nrtl: Nucleos(t)ide analogue. * Including 3 subjects from Cohort A randomized to Cohort E after Part 1 Week 16 visit

REFERENCES

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RESULTS

Safety and Tolerability

Table 2. Frequency and severity of treatment-emergent adverse effect

	BRII-179 (VBI-2601) 4x Q4W, cohort, dose				
	Cohort A Nrtl (n=5)	Cohort B 20μg+Nrtl (n=10)	Cohort C 20μg+IFN-α+Nrtl (n=10)	Cohort D 40μg+Nrtl (n=12)	Cohort E 40μg+IFN-α+Nrtl (n=12)
TEAEs	2(40.0)	7 (70.0)	10 (100.0)	10 (83.3)	11 (91.7)
Severe AE or SAE	0	0	0	0	0
Drug Related AE	0	6 (60.0)	9 (90.0)	8 (66.7)	11 (91.7)
TEAEs (any grade) in ≥2 patients in any treatment					
Fatigue	0	4 (40.0)	4 (40.0)	5 (41.7)	8 (66.7)
Headache	0	2 (20.0)	5 (50.0)	0	8 (66.7)
Injection site reaction	0	4 (40.0)	4 (40.0)	5 (41.7)	7 (58.3)
Myalgia	0	1 (10.0)	4 (40.0)	1 (8.3)	7 (58.3)
Pyrexia	0	0	3 (30.0)	0	6 (50.0)
Nasopharyngitis	0	0	0	3 (25.0)	0
Influenza like illness	1 (20.0)	1 (10.0)	2 (20.0)	0	1 (8.3)
Chills	0	0	2 (20.0)	0	1 (8.3)
Nausea	0	1 (10.0)	2 (20.0)	0	2 (16.7)
Diarrhea	0	0	2 (20.0)	0	2 (16.7)
Dizziness	0	1 (10.0)	0	0	2 (16.7)

TEAE: treatment-emergent adverse event; AE: Adverse event; Nrtl: Nucleos(t)ide analogue

- BRII-179 (VBI-2601) at 20 and 40μg admixed with low dose 3 MIU IFN-α in combination with Nrtl were generally safe and well tolerated in CHB patients (**Table 2**).
- No severe AEs, SAE, deaths, or signs of hepatotoxicity were reported.
- The most commonly reported AEs at least possibly drug related consisted of various AEs (e.g. fatigue, injection site reaction, headache, pyrexia, myalgia), which were mostly transient and of mild to moderate severity.
- Pyrexia, influenza like illness, chill, headache, nausea, diarrhea, and myalgia (known adverse events of interferon) occurred more frequently in subjects receiving BRII-179 (VBI-2601) admixed with 3MIU IFN-α than those receiving BRII-179 (VBI-2601) alone.
- There was no alanine aminotransferase (ALT) flare recorded.

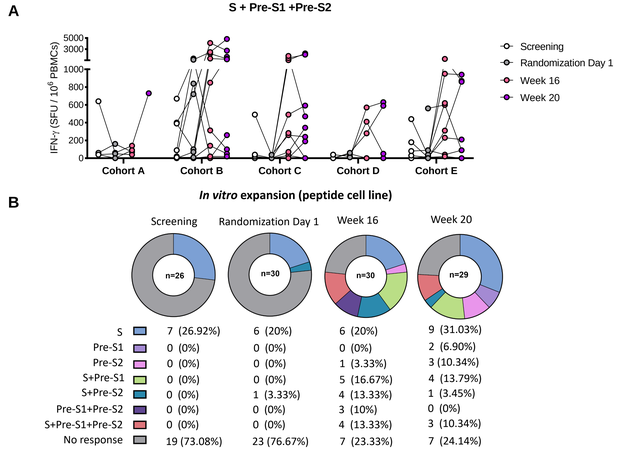
Changes in HBsAg

- Decreases in serum HBsAg level was limited post 4 doses of BRII-179 (VBI-2601) treatment. In most patients the decrease of HBsAg was minor (<0.2 log10).

BRII-179 (VBI-2601) induces HBV surface antigen specific T cells in chronic HBV patients

- In peptide expanded PBMCs, increased IFN-γ-producing Pre-S1-, Pre-S2- and S-specific T cells were detected in significant number of patients across treatment cohorts (**Table 3**).
- Significantly higher magnitudes of HBV antigen specific T cell responses were detected against all three peptide pools at week 16 after vaccination compared to pre-vaccination (**Figure 1A**).
- The majority of evaluable patients responded to at least one of the Pre-S1, Pre-S2 and S peptide pools after vaccination (overall 77% on week 16 and 76% at week 20) (**Figure 1B**).
- BRII-179 (VBI-2601) induced a detectable *ex vivo* response to HBV surface antigens in 4 out of 13 (31%) evaluable subjects who received BRII-179 (VBI-2601) admixed with IFN-α.

Figure 1. T cell responses to surface antigens in CHB patients post BRII-179 (VBI-2601) treatment



Magnitude (A) and breadth (B) of T cell response against Pre-S1, Pre-S2 and S, and the percentage of individuals with Pre-S1-, Pre-S2- and S-specific T cell responses by *in vitro* expansion ELISpot in evaluable CHB patients before and after BRII-179 (VBI-2601) vaccination. In (B) the T cell response was only assessed in evaluable subjects received BRII-179 (VBI-2601) treatment.

Table 3. Frequency of positive T cell responses (peptide cell line)

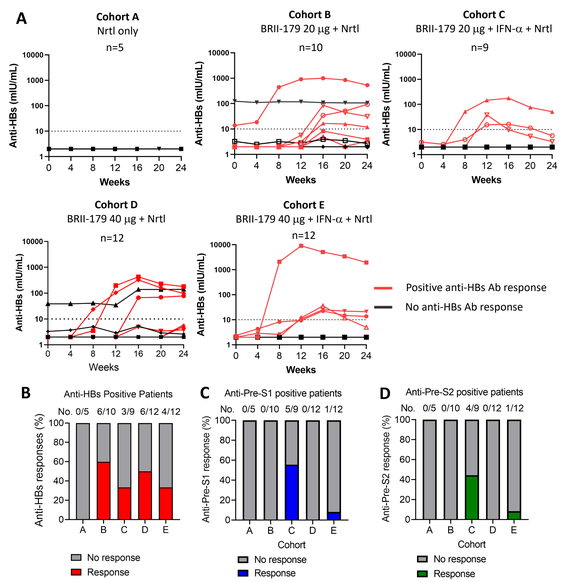
	Cohort A	Cohort B	Cohort C	Cohort D	Cohort E
	Nrtl (n=4)	20μg+Nrtl (n=9)	20μg+IFN-α+Nrtl (n=9)	40μg+Nrtl (n=4)	40μg+IFN-α+Nrtl (n=8)
Positive T cell response	0 (0%)	6 (67%)	7 (78%)	3 (75%)	4 (50%)

Positive T cell response: the quantity of spot forming units (SFU) post vaccination is at least 3 times the baseline of the maximum of pre-vaccination.

BRII-179 (VBI-2601) induces antibody responses to HBV surface antigens

- Boosting and/or restoration of anti-HBs antibodies was observed in 19/43 (44.2%) BRII-179 (VBI-2601) recipients, no clear differences across four treatment cohorts (**Figure 2A and 2B**).
- Anti-Pre-S1 and anti-Pre-S2 antibody responses were only detected in subjects who received BRII-179 (VBI-2601) admixed with IFN-α (**Figure 2C and 2D**).

Figure 2. Antibody responses to surface antigens in CHB patients post BRII-179 (VBI-2601) treatment



(A) Individual anti-HBs antibody titration over time in 5 cohorts. (B) The percentage of individuals with vaccine-induced positive anti-HBs antibody responses by cohorts. (C, D) The percentage of individuals with positive anti-PreS1 (C) or Pre-S2 (D) antibody responses by cohorts. Positive anti-HBs response was defined at any postbaseline visit with either (i) postbaseline anti-HBs ≥ 2 IU/L if anti-HBs undetectable at baseline or (ii) postbaseline anti-HBs ≥ 5 times the baseline anti-HBs if Baseline anti-HBs ≥ 2 IU/L.

CONCLUSION

- In this study in CHB patients under Nrtl therapy, both 20 and 40 μg of BRII-179 (VBI-2601) with/without low dose IFN-α administered through intramuscular injection were safe and well-tolerated.
- BRII-179 (VBI-2601) induced anti-HBs antibody response in >30% patients in all treated cohorts.
- BRII-179 (VBI-2601) also restored and/or boosted S-, Pre-S1-, Pre-S2-specific IFN-gamma producing T cells in the majority of treated patients evaluated.
- These data support further clinical evaluation of BRII-179 (VBI-2601) as an immunomodulator in combination with other treatment modalities for functional cure.

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CONTACT INFORMATION

Man-Fung Yuen, MD, PhD, DSc
Email: mfyuen@hku.hk