Received: 29 October 2020 | Revised: 14 January 2021 | Accepted: 8 February 2021

DOI: 10.1111/cts.13019

ARTICLE

Safety, tolerability, pharmacokinetics, and pharmacodynamics of HBM9161, a novel FcRn inhibitor, in a phase I study for healthy Chinese volunteers

Desmond Y. H. Yap[1,2] | **Jojo Hai**[1,3] | **Paul C. H. Lee**[1,4] | **Xueying Zhou**[5] | **Michael Lee**[5] | **Yu Zhang**[5] | **Meng Wang**[5] | **Xiaoxiang Chen**[5]

[1]Phase I Clinical Trials Centre, The University of Hong Kong, Hong Kong, Hong Kong

[2]Division of Nephrology, Department of Medicine, The University of Hong Kong, Hong Kong, Hong Kong

[3]Division of Cardiology, Department of Medicine, The University of Hong Kong, Hong Kong, Hong Kong

[4]Division of Endocrinology and Metabolism, Department of Medicine, The University of Hong Kong, Hong Kong, Hong Kong

[5]Harbour Biomed, Inc., Shanghai, China

Correspondence
Desmond Y. H. Yap, NCB 301, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong.
Email: desmondy@hku.hk

Funding information
Harbour Biomed, Inc., Shanghai, China, sponsored this clinical trial. Dr. Desmond Y.H. Yap also received donations from Wai Im Charitable Foundation and Chan Sui Kau Family Benefits and Charitable Foundation.

Abstract

Blockade of the binding between neonatal Fc receptor and IgG-Fc reduces circulating IgG, and thus emerges as a potential therapy for IgG-mediated autoimmune conditions. This was a double blind, randomized, single ascending dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of HBM9161 (a fully humanized Fc receptor monoclonal antibody) in healthy Chinese volunteers. Subjects were randomized to receive a single s.c. dose of HBM9161 or placebo in a 3:1 ratio in 3 dosing cohorts (340 mg, 510 mg, or 680 mg, respectively), and then followed up for 85 days. Study end points included incidence of adverse event (AE), serum drug concentration, IgG and its subclasses, and anti-drug antibodies (ADAs). Twenty-four subjects were randomized. Dose-dependent reduction of total IgG occurred rapidly from baseline to reach nadir at day 11, then recovered steadily from day 11 to day 85. The mean maximum percentage reductions from baseline total IgG were 21.0 ± 9.3%, 39.8 ± 5.13%, and 41.2 ± 10.4% for subjects receiving HBM9161 340 mg, 510 mg, and 680 mg, respectively. The exposure of HBM9161 (areas under the curve [AUCs] and peak plasma concentration [C_{max}]) increased in a more than dose-proportional manner at the dose examined. All reported AEs were mild in severity. The most reported AEs in the HBM9161 groups were influenza-like illness and rash. Two subjects developed ADA during the study period. A single s.c. dose of HBM9161 results in sustained and dose-dependent IgG reduction, and was well-tolerated at a dose up to 680 mg in Chinese subjects. The data warrant further investigation of its effects in IgG-mediated autoimmune disorders.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Animal studies and recent human data from White populations showed that treatment with neonatal Fc receptor (FcRn) inhibitor reduces circulating IgG levels and is well-tolerated. Data of FcRn inhibitors in Asians is relatively limited.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study investigated the pharmacokinetics (PKs), pharmacodynamics (PDs), and safety profile of HBM9161 (an FcRn inhibitor) in healthy Chinese volunteers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Subcutaneous HBM9161 is safe and effective in IgG reduction in Chinese subjects. The PKs, PDs, and safety characteristics in Chinese are similar to the first-in-human study in the White population.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

HBM9161 can be a potential treatment for IgG-mediated autoimmune disorders and organ transplant rejection.

INTRODUCTION

Autoimmune diseases are characterized by the failure to distinguish between self and non-self antigens by the immune system, which results in attack to normal constituents of various organ systems. Autoreactive IgG antibodies play a central role in the pathogenesis of many autoimmune disorders such as myasthenia gravis (MG), immune thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), and Graves' ophthalmopathy (GO).[1–4] The immunological insults in these autoimmune conditions may arise from direct binding of pathogenic IgG to the target antigens, or mediated through immune complex formation that activates inflammatory or complement cascades.[5] Various strategies have been attempted to reduce pathogenic IgG autoantibodies in these diseases, which include direct depletion of B cells by monoclonal antibodies that bind to cell surface molecules (e.g., CD20), inhibition of B cell survival factors (e.g., BAFF), nonspecific binding of pathogenic IgG by exogenous immunoglobulins/preventing it from binding to neonatal Fc receptor (FcRn; via saturation of FcRn), thus accelerating degradation (e.g., i.v. immunoglobulin) or extracorporeal removal of autoantibodies (e.g., plasmapheresis).[6–11] Notwithstanding, efficacy and safety issues remain important concerns that limit the use of these agents and, hence there is still unmet need for treatment that can effectively and safely reduce circulating IgG in different medical conditions. In this context, the inhibition of FcRn presents a promising approach to decrease circulating IgG in autoimmune diseases. FcRn was initially recognized to mediate transfer of maternal IgG to neonates, but subsequent studies demonstrated that it also plays a pivotal role in the recycling of IgG.[12,13] The level of IgG circulating is maintained by both production and recycling. FcRn prevents degradation of IgG in lysosome by binding to the proteins and transporting them from the sorting endosome to the cell surface, and thus the blockade of IgG-FcRn interaction results in enhanced degradation and clearance of IgG.[14–19] Following the idea that the blockade of interaction of FcRn with pathogenic IgG, antibodies which can directly bind and inhibit FcRn (e.g., rozanolixizumab and efgartigimod) have been developed. Currently, both antibodies have been tested in phase II/III clinical studies, with the accumulation of efficacy and safety data in human beings.

HBM9161 (RVT-1401) is a fully human monoclonal IgG1 antibody that targets FcRn. The Fc portion of this IgG1 has been modified to decrease the potential for antibody-dependent cell-mediated cytotoxicity. Previous animal data from monkeys suggested that HBM9161 could effectively diminish circulating IgG levels and was well-tolerated.[20] The first-in-human study of HBM9161 in the White populations in Australia and Canada showed that the drug was well-tolerated.[21] However, there are limited data regarding the efficacy and safety of HBM9161 in Asians. Here, we reported the pharmacokinetics (PKs), pharmacodynamics (PDs), and safety profile of HBM9161 in Chinese healthy volunteers.

METHODS

Study design

This was a phase I, randomized, double-blinded, placebo-controlled study to investigate the safety, tolerability, PKs, and PDs of single ascending doses of HBM9161 in healthy Chinese subjects. Subjects were randomized to receive a single s.c. dose of HBM9161 or placebo (same formulation as study drug, without active ingredients; 100 mM L-Histidine/Histidine HCl, 100 mM L-Arginine HCl, and 0.02% Polysorbate 20, pH 6.0) in a 3:1 ratio (i.e., 6 receiving HBM9161 and 2 receiving placebo) in three dosing cohorts (dose level of 340 mg, 510 mg, or 680 mg, respectively). Each subject only participated in one dosing cohort. Safety and PD (total IgG) data were reviewed prior to the next dose escalation. The dose level was allowed to be adjusted during the study based on the preliminary results. All subjects were screened within 40 days prior to study drug administration. Eligible subjects checked in on day –1 and remained confined to the study center until day 5. Subjects returned for follow-up

visits and for an "End of Study Visit" (day 85) per the Time and Events Table. Subject who had persistent anti-HBM9161 antibodies after day 85 was requested to have blood samples drawn for anti-HBM9161 antibody test and was assessed for adverse events (AEs) at ~ 6, 9, or 12 months after dosing until 2 consecutive samples had been confirmed to be negative for anti-HBM9161 antibody. This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice and the Declaration of Helsinki, and informed consent was obtained from each subject before any study-specific procedures were performed. This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 19-299) and also registered at ClinicalTrials.gov (NCT number: NCT03971916).

Screening and study entry criteria

The inclusion criteria were: (1) Han Chinese male or female subjects who are 18 to 45 (inclusive) years of age, and had provided written consent, been willing and able to comply with all study procedures; (2) subjects with good health with no clinically significant abnormalities as determined by medical history, physical examination, 12–lead electrocardiogram (ECG) and clinical laboratory tests; (3) body weight greater than 50 kg with body mass index greater than or equal to 19.0 and less than 24.0 kg/m^2.

Exclusion criteria were: (1) presence of any concomitant clinically significant diseases, including cardiovascular, gastrointestinal, endocrinological, hematological, hepatic, immunological, metabolism, urological, pulmonary, neurological, dermatological, psychiatric, renal, or other major disease or malignancy, as judged by the investigator; (2) total IgG level of less than 700 mg/dl (test results from local laboratory) at screening; (3) evidence of active infection (e.g., sepsis, pneumonia, and abscess) or had a serious infection, or fungal (noncutaneous) infection within 1 week prior to admission (day −1); (4) consumption of prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days or less than 5 half-lives (whichever is longer) of the respective drug prior to dosing of the study drug.

Safety analysis

Safety was evaluated by assessment of clinical laboratory tests, physical examinations, vital sign measurements, and ECG readings at various timepoints during the study, and by the documentation of AEs, including severity of local reactions. Safety data from subjects who received placebo was pooled. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0. AEs were followed up until they resolved, had stable sequelae, determined by the investigator to be no longer clinically significant, or lost to follow-up. As to causality, "possibly related" is defined as there is a clear temporal sequence of the AE onset relative to the administration of study drugs, and potential alternative etiology is not apparent, "possible unrelated" is defined as a temporal sequence of the AE onset relative to the administration of study drugs is not clear, alternative causes are also possible, whereas "unrelated" is defined as there is no temporal sequence of the AE onset relative to the administration of study drugs, and/or there is evidence of other causes, such as concurrent medication or illness that contributed to the event.

PK analysis

Blood samples for PK analysis of HBM9161 was collected at the timepoints of predose and at 2, 4, 8, 12, 24, 36, and 48 h after injection, and on days 4, 5, 8, and 11. Serum concentrations of HBM9161 was determined using fully validated enzyme-linked immunosorbent assay method. Briefly, HBM9161 was captured by biotinylated drug target (biotin-shFcRn), bound HBM9161 was then detected with an anti-HBM9161 secondary antibody followed by HRP-labeled anti-rabbit antibody. The bound HRP is then detected by addition of TMB solution, once a proper optical density is achieved, color development is stopped with acid. The absorbance is then read on a SpectraMax plate reader. HBM9161 concentrations were calculated by interpolation on a standard curve. The lower and upper limits of quantification of the assay were 10.0 ng/ml and 1600 ng/ml respectively. Raw data were archived at the bioanalytical site.

PD analysis

Blood samples for PD analysis were collected for measurement of total IgG and albumin before dosing on day 1, then on days 2, 3, 4, 5, 8, 11, 15, 22, 29, 43, 57, and 85 after drug administration. Samples for IgG subclasses, IgM, and IgA was collected predose on day 1, and at days 8, 15, 29, 43, and 57. All the samples were collected, labeled, stored, and shipped in accordance with the laboratory manual.

ADA analysis

Blood samples for antidrug antibody (ADA) analysis were collected before dosing, then at days 8, 15, 29, 57, and 85 after drug administration. Anti-HBM9161 antibodies were determined in serum samples using fully validated electrochemiluminescent (ECL) qualitative assay. Briefly, an

Affinity Capture Elution assay is applied, affinity capture of ADA on solid-phase drug followed by removal of excess free drug, release, and transfer of bound ADA and subsequent detection using biotinylated drug, streptavidin-Sulfo-Tag is sequentially added to detect the anti-HBM9161 antibodies in the sample. Following incubation of detection reagents, read buffer containing tripropylamine is added, which causes the ruthenium to produce a chemiluminescent signal that is triggered when voltage is applied, the ECL signal is in proportion to the amount of anti-HBM9161 antibodies, ADA analysis follows 3-tiered testing approach. Raw data were archived at the bioanalytical site.

Study objectives and end points

The primary study objective was to evaluate the safety and tolerability of HBM9161 following a single s.c. dose in healthy subjects as assessed by drug-related AEs, with the number (N [%]) of subjects with drug-related AEs as the primary end point. The secondary study objective was to evaluate the safety and tolerability of HBM9161 following a single s.c. dose in healthy subjects as assessed by other AE variables, and to evaluate the PKs of HBM9161 following the s.c. dose in healthy subjects, with following secondary end points: other variables for safety and tolerability assessments, including the number (N [%]) of subjects with AEs, abnormal 12-lead ECG, abnormal clinical laboratory tests, abnormal physical examination, and change of vital signs (blood pressure and pulse rate) from baseline; PK parameters, including peak plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the curve from zero to infinity ($AUC_{0-\infty}$), terminal half-life ($t_{1/2}$), total apparent clearance (CL/F), and volume of distribution based on the terminal phase (Vz/F). PDs (change in serum concentrations of IgG and albumin) of HBM9161 and measure ADA following a single s.c. dose in healthy subjects, with PD parameters as the other end points.

Statistical methods

The sample size of 24 subjects (8 per cohort [HBM9161 vs. placebo: 6:2]) was considered sufficient for the assessment of PK parameters in Chinese healthy subjects while exposing as few subjects as possible to the investigational product and study procedures. All subjects who received study medication were included in the safety, PK/PD, and biomarker analysis. Subjects' data were analyzed according to the treatment actually received, regardless of their randomized treatment assignment. Final analysis would include data up to day 85. Unless stated otherwise, descriptive summaries for continuous variables were expressed as mean (SE). Categorical variables were expressed as frequency and percentages.

Only treatment emergent AEs (TEAEs), which onset at or after the start of study medication administration, were included in the AE summary.

For PK evaluation, serum drug concentration-time data was analyzed by noncompartmental methods with Thermo ScientificTM Kinetica. Calculations were based on the actual sampling times recorded during the study. From the serum concentration-time data, the following PK parameters were determined: $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, CL/F, and Vz/F. Additional PK parameters were calculated based on data. Dose proportionality of C_{max} and $AUC_{0-\infty}$ were assessed graphically and statistically as appropriate using a power model.

PD data included serum concentrations of IgG (total, and by class and subclass) and albumin. Exploratory biomarker data included serum concentrations of C-reactive protein (hs-CRP) and serum complement (CH50, C3).

RESULTS

Phase I study in healthy volunteers

Twenty-four healthy Han Chinese subjects were randomized in three different dosing cohorts (6 receiving HBM9161 and 2 receiving placebo in each cohort; Table 1). All subjects completed the study without early discontinuation.

Safety

A total of 39 TEAEs were reported during the study (Table 2). At least one TEAE was reported in 5 (83.3%), 5 (83.3%), 5 (83.3%), and 2 (33.3%) subjects receiving placebo, HBM9161 340 mg, 510 mg, and 680 mg, respectively. The reported TEAEs were neither injection site reactions nor drug-related liver injury. None of the reported TEAEs was serious or severe (severity higher than grade 2). No subject was discontinued from the study due to AEs. All TEAEs had resolved at the last study visit, except for a nondrug-related asymptomatic bacteriuria, which occurred in one subject in the HBM9161 510 mg cohort.

Among the 39 TEAEs reported, 33 were considered either not related or possibly not related to the use of the study drug. The remaining 6 drug-related TEAEs were reported by 4 subjects, which included rash in 3 subjects receiving HBM9161 (one in each dosing cohort), rash pruritic in one subject receiving HBM9161 (510 mg), and pruritus and constipation in one subject receiving HBM9161 (680 mg). All drug-related TEAEs were mild in severity (grade 1). The most frequently reported TEAE in this study was influenza like illness (ILI), which occurred in eight subjects (5 in the HBM9161 510 mg

TABLE 1 Demographic and baseline clinical characteristics of 24 healthy subjects who have received HBM9161 or placebo

		HBM9161		
	Placebo (*N* = 6)	**340 mg (*N* = 6)**	**510 mg (*N* = 6)**	**680 mg (*N* = 6)**
Age, year				
Mean (SD)	25 (6.3)	25 (8.0)	27 (8.8)	24 (3.0)
Min, Max	19, 34	20, 41	19, 38	21, 27
Sex				
Female	2 (33.3%)	3 (50.0%)	4 (66.7%)	3 (50.0%)
Male	4 (66.7%)	3 (50.0%)	2 (33.3%)	3 (50.0%)
Race and ethnicity				
Asian – Han Chinese	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)
Body weight, kg				
Mean (SD)	62.6 (9.43)	62.4 (6.72)	58.6 (7.67)	60.9 (8.80)
Min, Max	50.8, 73.0	52.7, 72.2	50.1, 69.9	51.5, 75.5
BMI, kg/m^2				
Mean (SD)	22.0 (1.07)	21.6 (1.20)	21.3 (1.19)	21.0 (1.55)
Min, Max	20.8, 23.7	20.3, 23.3	20.2, 23.4	19.0, 23.1
Total IgG (Local Lab) g/L				
Mean (SD)	11.59 (1.082)	10.76 (1.020)	12.50 (2.820)	11.43 (1.403)
Min, Max	9.48, 12.58	9.52, 12.19	10.10, 17.56	9.59, 13.41
Albumin (Local Lab) g/L				
Mean (SD)	44 (1.5)	44 (1.8)	43 (1.8)	45 (1.6)
Min, Max	42, 46	42, 47	40, 45	42, 46

Abbreviation: BMI, body mass index.

cohort). All these ILIs were considered not related to the drug and recovered without alteration of the drug dosage by the investigator (Table 2). All TEAEs graded as moderate in severity were considered as possibly nondrug-related, which included herpes zoster in one patient receiving placebo, influenza-like illness in one subject receiving HBM9161 (510 mg), asymptomatic bacteriuria in one subject receiving HBM9161 (510 mg), vomiting in one subject receiving HBM9161 (680 mg), and diarrhea in one subject receiving HBM9161 (680 mg).

Most results of the safety blood tests were either normal or abnormal without clinically significance. Two subjects who received HBM9161 (340 mg) and one subject who received placebo showed elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) that were considered clinically significant and reported as AEs. The elevated AST and ALT were considered nondrug-related and therefore were not regarded as drug-induced liver injury.

Pharmacokinetics

The PKs data of patients receiving a single s.c. dose of HBM9161 (340 mg, 510 mg, or 680 mg) are summarized in Figure 1 and Table 3. The mean C_{max} of HBM9161 were 2980 ± 4610 ng/ml, 21,100 ± 18,200 ng/ml, and 30,300 ± 21,800 ng/ml in subjects receiving 340 mg, 510 mg, and 680 mg, respectively. The median T_{max} (range) of HBM9161 were 33.0 (24.2–72) h, 72.1 (48.0–168) h, and 83.9 (72.2–96.0) h in subjects receiving 340 mg, 510 mg, and 680 mg, respectively. The mean $AUC_{0\text{-}t}$ of HBM9161 were 171,000 ± 241,000 h*ng/ml, 1,940,000 ± 1,620,000 h*ng/ml, and 3,300,000 ± 2,540,000 h*ng/ml, in subjects receiving 340 mg, 510 mg, and 680 mg, respectively. The mean $AUC_{0-\infty}$ of HBM9161 were 172,000 ± 241,000 h*ng/ml, 2,320,000 ± 1,480,000 h*ng/ml, and 4,230,000 ± 2,160,000 h*ng/ml, in subjects receiving 340 mg, 510 mg, and 680 mg, respectively.

Based on the results of power model, the 95% confidence interval for the slopes (β) for $AUC_{0\text{-}t}$, $AUC_{0-\infty}$, and C_{max} were 2.41–7.95, 3.64–8.76, and 1.73–7.52, respectively, indicating the exposure of HBM9161 increased more than proportional to the dose.

Pharmacodynamics

For subjects receiving 340–680 mg HBM9161, the mean total IgG decreased rapidly from baseline to reach nadir at day 11 and then recovered steadily from day 11 to day 85.

TABLE 2 Overview of TEAEs and summary of TEAEs by SOC and PT (all causalities)

	Placebo			HBM9161 340 mg			HBM9161 510 mg			680 mg HBM9161		
	Male	Female	All genders	Male	Female	All genders	Male	Female	All genders	Male	Female	All genders
Subjects with AEs, No. of Subject (%)	3 (100.0)	2 (100.0)	5 (100.0)	3 (100.0)	2 (100.0)	5 (100.0)	2 (100.0)	3 (100.0)	5 (100.0)	1 (100.0)	1 (100.0)	2 (100.0)
Subjects with SAEs, *N* of subjects (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects discontinued due to AE, *N* of subjects (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. of AEs	9 (100.0)	4 (100.0)	13 (100.0)	5 (100.0)	3 (100.0)	8 (100.0)	2 (100.0)	10 (100.0)	12 (100.0)	1 (100.0)	5 (100.0)	6 (100.0)
Severity, all AEs, no. of AEs (%)												
Grade 1	8 (88.9)	4 (100.0)	12 (92.3)	5 (100.0)	3 (100.0)	8 (100.0)	1 (50.0)	6 (60.0)	7 (58.3)	1 (100.0)	3 (60.0)	4 (66.7)
Grade 2	1 (11.1)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	4 (40.0)	5 (41.7)	0 (0.0)	2 (40.0)	2 (33.3)
Severity, drug-related, no. of AEs (%)												
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (12.5)	0 (0.0)	2 (20.0)	2 (16.7)	0 (0.0)	3 (60.0)	3 (50.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Relationship to study drug, no. of AEs (%)												
No reasonable possibility	9 (100.0)	4 (100.0)	13 (100.0)	5 (100.0)	2 (66.7)	7 (87.5)	2 (100.0)	8 (80.0)	10 (83.3)	1 (100.0)	2 (40.0)	3 (50.0)
Reasonable possibility	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (12.5)	0 (0.0)	2 (20.0)	2 (16.7)	0 (0.0)	3 (60.0)	3 (50.0)

System organ class/preferred term	Placebo			HBM9161 340 mg			HBM9161 510 mg			680 mg HBM9161		
	Male	Female	All genders	Male	Female	All genders	Male	Female	All genders	Male	Female	All genders
No. of subjects	4 (100.0)	2 (100.0)	6 (100.0)	3 (100.0)	3 (100.0)	6 (100.0)	2 (100.0)	4 (100.0)	6 (100.0)	3 (100.0)	3 (100.0)	6 (100.0)
Total with at least one AE	3 (100.0)	2 (100.0)	5 (100.0)	3 (100.0)	2 (100.0)	5 (100.0)	2 (100.0)	3 (100.0)	5 (100.0)	1 (100.0)	1 (100.0)	2 (100.0)
Gastrointestinal disorders	2 (66.7)	0 (0.0)	2 (40.0)	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
Abdominal pain	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (33.3)	0 (0.0)	1 (20.0)	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
Noninfective gingivitis	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
Nervous system disorders	0 (0.0)	2 (100.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	2 (100.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

(Continues)

TABLE 2 Continued

System organ class/preferred term	Placebo			HBM9161 340 mg			HBM9161 510 mg			680 mg HBM9161		
	Male	Female	All genders	Male	Female	All genders	Male	Female	All genders	Male	Female	All genders
General disorders and administration site conditions	0 (0.0)	1 (50.0)	1 (20.0)	0 (0.0)	1 (50.0)	1 (20.0)	2 (100.0)	3 (100.0)	5 (100.0)	1 (100.0)	0 (0.0)	1 (50.0)
Influenza like illness	0 (0.0)	1 (50.0)	1 (20.0)	0 (0.0)	1 (50.0)	1 (20.0)	2 (100.0)	3 (100.0)	5 (100.0)	1 (100.0)	0 (0.0)	1 (50.0)
Malaise	0 (0.0)	1 (50.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypersensitivity	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asymptomatic bacteriuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	1 (33.3)	0 (0.0)	1 (20.0)	2 (66.7)	0 (0.0)	2 (40.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	1 (33.3)	0 (0.0)	1 (20.0)	2 (66.7)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	1 (33.3)	0 (0.0)	1 (20.0)	2 (66.7)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Human chorionic gonadotropin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and s.c. tissue disorders	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	2 (100.0)	2 (40.0)	0 (0.0)	2 (66.7)	2 (40.0)	0 (0.0)	1 (100.0)	1 (50.0)
Rash	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	2 (100.0)	2 (40.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	1 (100.0)	1 (50.0)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (50.0)
Rash pruritic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry throat	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse events; PT, preferred term; SOC, system organ class; TEAEs, treatment emergent adverse events.

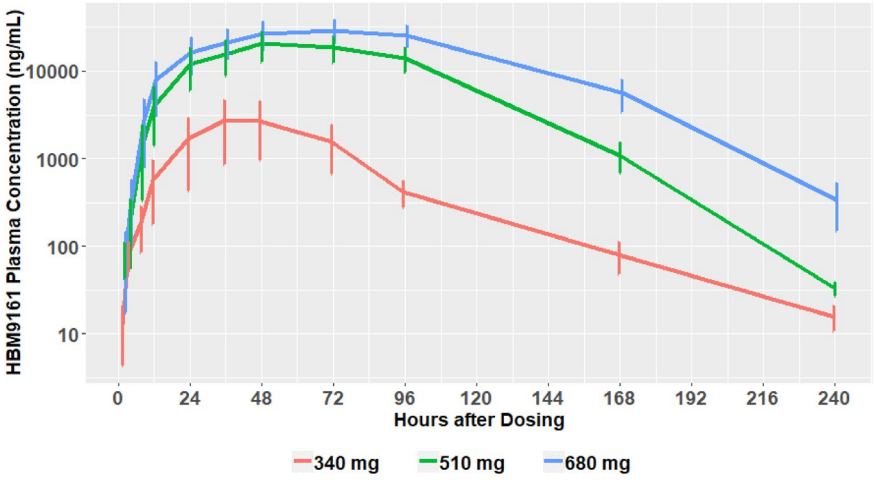

FIGURE 1 The changes in drug concentration over time in health subjects receiving a single s.c. dose of HBM9161 at 340 mg, 510 mg, and 680 mg, respectively (semi-logarithmic scale). Plasma concentration–time profiles for HBM9161 by s.c. administration. Healthy subjects were dosed with 340 mg, 510 mg, or 680 mg HBM9161 (6 subjects per dosing cohort) or placebo (2 subject per dosing cohort), by s.c. administration. Values are shown as mean ± SE

TABLE 3 Summary of PK data in subjects who have received a single s.c. dose of HBM9161

	HBM9161 (340 mg) (*N* = 6)	HBM9161 (510 mg) (*N* = 6)	HBM9161 (680 mg) (*N* = 6)
Mean C_{max} (±SD) ng/ml	2980 (±4610)	21,100 (±18,200)	30,300 (±21,800)
Median T_{max} h (range)	33.0 (24.2–72)	72.1 (48.0–168)	83.9 (72.2–96.0)
Mean $AUC_{0\text{-}t}$ (±SD) h*ng/ml	171,000 (±241000)	1,940,000 (±1,620,000)	3,300,000 (±2,540,000)
Mean $AUC_{0\text{-}\infty}$ (±SD) h*ng/ml	172,000 (±241000)	2,320,000 (±1,480,000)	4,230,000 (±2,160,000)
$t_{1/2}$ (±SD) h	37.9 (±20.9)	16.9 (±2.53)	14.8 (±0.884)
CL/F (±SD) mL/h	11,900 (±18600)	308 (±188)	214 (±155)
Vz/F (±SD) ml	1,070,000 (±1,980,000)	7960 (±5820)	4710 (±3710)

Abbreviations: $AUC_{0-\infty}$, area under the curve from zero to infinity; AUC_{0-t}, area under the concentration-time profiles; CL/F, total apparent clearance; C_{max}, peak plasma concentration; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; T_{max}, time to peak plasma concentration; Vz/F, volume of distribution based on the terminal phase.

The mean total IgG remained steady from baseline to day 85 in subjects receiving placebo. The maximum reductions from baseline in total IgG were dose-dependent and occurred at day 11 for all dose levels of HBM9161, were significantly lower than those receiving placebo. The mean maximum percentage reductions from baseline total IgG were 21.0 ± 9.3%, 39.8 ± 5.13%, and 41.2 ± 10.4% for subjects receiving HBM9161 340 mg, 510 mg, and 680 mg, respectively, compared with that of 5.54 ± 6.42% in placebo (Figure 2). The changes of different IgG subclasses, IgA and IgM are shown in Figures 3, S1, and S2.

For subjects receiving 340–680 mg HBM9161, there was a downward fluctuation of the mean albumin from baseline to day 11 and then it recovered fully from day 11 to day 85. For subjects receiving placebo, there was a slightly upward trend for the mean albumin from baseline to day 85. The maximum reductions from baseline in albumin were dose-dependent and occurred at day 5 for 340 mg and at day 11 for subjects receiving 510 mg and 680 mg, respectively (Figure 4).

Two subjects presented with high level of hs-CRP. One subject receiving HBM9161 (510 mg) showed elevated CRP at 521.9 nmol/L at day 29, and assessments of hs-CRP prior to day 29 were within the normal range. Another subject receiving HBM9161 (510 mg) showed elevated hs-CRP (181–1227.6 nmol/L) at day 2 (181.0 nmol/L), 4 (1227.6 nmol/L), and 8 (357.2 nmol/L). Both subjects suffered from ILI at the time of laboratory assessments. Two and one subjects had abnormally high results of IgA, of whom one subject receiving HBM9161 340 mg showed IgA elevation higher than 2 times the upper limit of normal (IgA: 8.23 g/L at day 8). Subjects receiving HBM9161 and placebo did not show difference in the serum C3 levels and its classical pathway at days 2 and 8.

There were two subjects who developed immunogenic responses to the study drug. One subject in HBM9161 680 mg

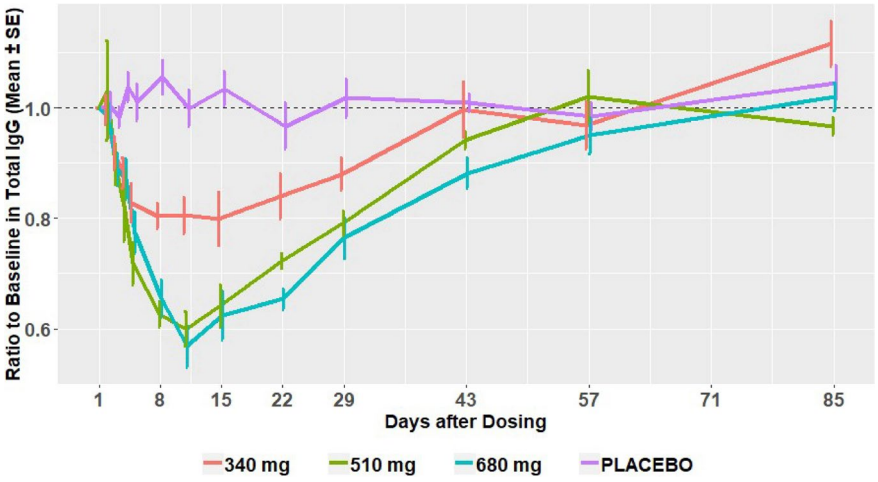

FIGURE 2 The changes of total IgG concentration over time in health subjects receiving a single s.c. dose of HBM9161 at 340 mg, 510 mg, and 680 mg, respectively. Mean percentage change from baseline in serum IgG concentrations over time, after a single dose of HBM9161 s.c. administration. Baseline is defined as the predose day 1 concentration. Mean percentage change and SE are shown; $n = 6$ for placebo and each HBM9161 group

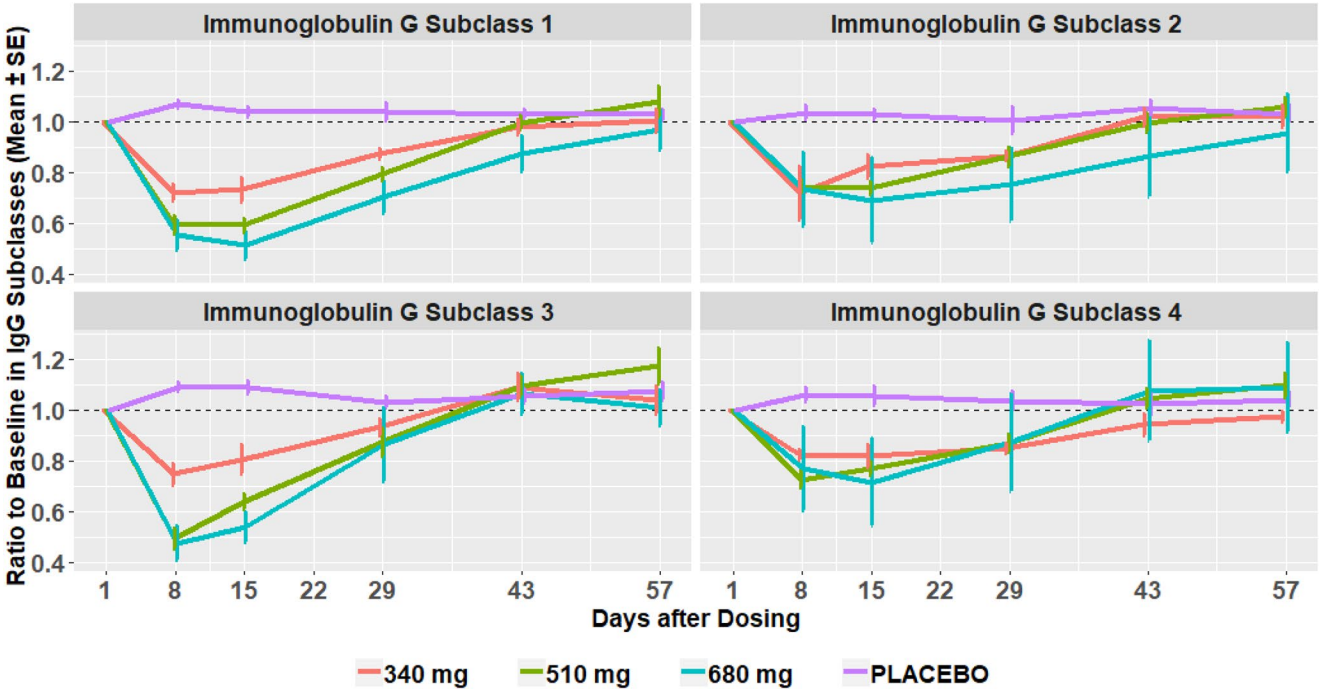

FIGURE 3 The changes of different IgG subclasses over time in health subjects receiving a single s.c. dose of HBM9161 at 340 mg, 510 mg, and 680 mg, respectively. Serum concentrations of IgG1, IgG2, IgG3, and IgG4 after a single dose of placebo or HBM9161 by s.c. administration. Mean percentage change and SE are shown; $n = 6$ for placebo and each HBM9161 group

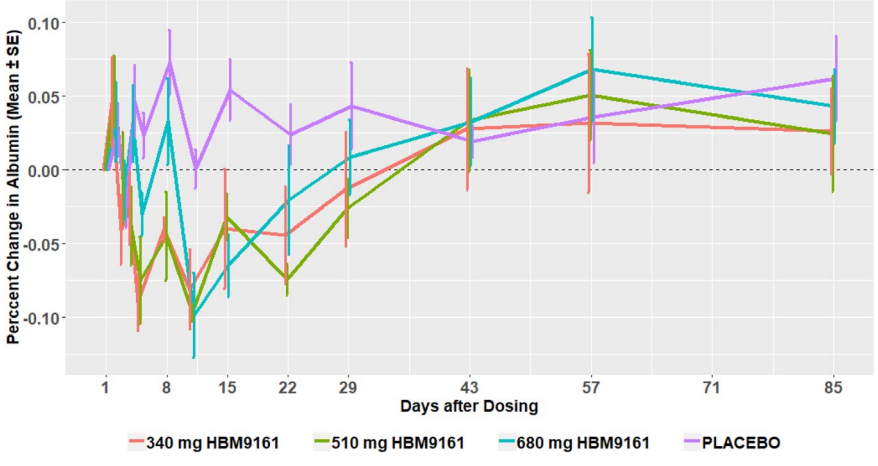

FIGURE 4 The changes of albumin concentration over time in health subjects receiving a single s.c. dose of HBM9161 at 340 mg, 510 mg, and 680 mg, respectively. Mean percentage change from baseline in serum albumin concentrations over time, after a single dose of HBM9161 s.c. administration. Baseline is defined as the predose day 1 concentration. Mean percentage change and SE are shown; $n = 6$ for placebo and each HBM9161 group

showed seropositivity for ADA at day 57, which was seronegative at day 85. Another subject in HBM9161 680 mg showed persistent seropositivity for ADA at day 57 and day 85, but the results became negative at 6 and 9 months postdose.

DISCUSSION

Pathogenic IgG plays important roles in various medical conditions, such as autoimmune diseases and organ transplant rejections.[22] FcRn shows crucial function in maintaining the level of IgG in circulation, and thus suppression of IgG levels by FcRn inhibition presents a novel and attractive approach to treat immunoglobulin-mediated diseases. HBM9161, is a fully human monoclonal antibody that targets FcRn. Data from the first-in-human study of HBM9161 in healthy White volunteers showed that the drug was well-tolerated following both single (i.v. and s.c.) and multiple doses (s.c.), and was associated with rapid and sustained reduction of total IgG and IgG subclasses following multiple s.c. injections.[21] In this study, we reported the PKs, PDs, and safety profiles of HBM9161 in Chinese healthy subjects after a single s.c. dose.

Our current data suggested that following a single s.c. dose of HBM9161, total IgG levels decreased rapidly to reach nadir at day 11, then recovered steadily from day 11 to day 85. Such effect is consistent across the different doses tested in our study (i.e., 340 mg, 510 mg, and 680 mg). The dose-dependent mean maximum reductions in serum IgG antibody levels were between 21.0% and 41.2%. The different IgG subclasses also showed a similar pattern as the total IgG levels following a single s.c. dose of HBM9161. Such pharmacological properties are attractive for autoimmune diseases and organ transplant rejections, in which rapid and sustained reduction of pathogenic IgG are required for disease control. Unlike some other therapies that target at the B cell repertoire, FcRn inhibitor does not cause B cell depletion and IgG levels generally recover within 3 months. This may potentially reduce prolonged immunosuppression and long-term serious infective complications. The changes of total IgG and IgG subclasses observed in this study were in line with the data in the phase I clinical trial in Australia and Canada, although subjects in previous studies received multiple-ascending doses (MADs) of HBM9161 and both i.v. and s.c. administrations.[21] Whether an MAD schedule and different routes of administration would produce the same pharmacologic effects in Chinese subjects remain unclear, and future studies that investigate these issues are warranted.

Following s.c. administration of HBM9161, the median time to peak concentrations ranged from approximately one and a half days for the lowest dose administered (340 mg) to over 3 days for the highest dose of 680 mg. Similar PK profiles were also observed in the first-in-human study in Australia and Canada.[21] Our present data suggested that the exposure of HBM9161 increased more than proportional to the dose, which may be due to the target mediated drug disposition (TMDD) as a therapeutic protein. However, due to the large variability for exposure as well as for the half-life, a solid conclusion cannot be made solely from data in this study. Because we have only limited PK data, population-based PK model analysis is not feasible at this stage. However, the population approach will be utilized to pooled data from other on-going and planned studies to analyzed PK characteristic of HB9161 including TMDD and covariant effects.

Our present findings also suggested that HBM9161 was safe and well-tolerated across the three dose ranges tested in this study, in line with the safety profiles shown in the White population. The incidence of TEAEs in patients receiving HBM9161 was similar to those receiving placebo. The most frequently reported TEAEs in this study was ILI, which was generally mild and recovered without alteration of the drug dosage by the investigator. There was also no serious AEs noted in this study. Our results also suggested that single s.c. dose of HBM9161 treatment did not lead to significant changes in serum albumin levels, IgA, IgM, and complements. Two subjects in the HBM9161 (680 mg) cohort developed ADA, and one subject's ADA response was negative at month 3 and the other subject's ADA response was negative at month 6s and 9 postdosing. Within the range of dose studied, PKs/PDs parameters were not influenced by ADA response, however, the impact of ADA on the PKs and PDs of HBM9161 remains to be elucidated in subsequent studies. Although it is important to compare the ADA response of HBM9161 with other drugs currently being developed, such comparison remains difficult as the assays for detecting ADA vary between different studies.

CONCLUSION

In general, our data demonstrates the similar PK, PD, and safety characteristics to the first-in-human study in the White population. Our results support that s.c. HBM9161 is safe and effective in IgG reduction in Chinese subjects, and thus is a promising candidate for the treatment of IgG-mediated autoimmune diseases (e.g., MG, ITP, SLE, and GO) as an alternative to the current standard-of-care treatments. Several phase II studies are underway to test this novel therapeutic strategy in patients with MG (NCT04346888) and ITP (NCT04428255). Apart from autoimmune diseases, other therapeutic potentials of HBM9161 include the prevention or control of rejection in organ transplant recipients.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

D.Y.H.Y. designed and performed the research, analyzed the data, and wrote the manuscript. J.H. and P.C.H.L. performed the research. X.Z., M.L., Y.Z., M.W., and X.C. analyzed the data and wrote the manuscript.

REFERENCES

1. Cetin H, Vincent A. Pathogenic mechanisms and clinical correlations in autoimmune Myasthenic syndromes. *Semin Neurol*. 2018;38(3):344-354.
2. Zufferey A, Kapur R, Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). *J Clin Med*. 2017;6(2):16.
3. Salaman M. Two paradoxes and a surprise on the road to an understanding of systemic lupus erythematosus. *Immunol Lett*. 2012;148(1):49-52.
4. Wiersinga W. Autoimmunity in Graves' ophthalmopathy: the result of an unfortunate marriage between TSH receptors and IGF-1 receptors? *J Clin Endocrinol Metab*. 2011;96(8):2386-2394.
5. Sinha AA, Lopez MT, McDevitt HO. Autoimmune diseases: the failure of self tolerance. *Science*. 1990;248(4961):1380-1388.
6. Pescovitz M. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant*. 2006;6(5 Pt 1):859-866.
7. Samy E, Wax S, Huard B, Hess H, Schneider P. Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases. *Int Rev Immunol*. 2017;36(1):3-19.
8. Zuercher AW, Spirig R, Baz Morelli A, Käsermann F. IVIG in autoimmune disease - potential next generation biologics. *Autoimmun Rev*. 2016;15(8):781-785.
9. Alamartine E, Maillard N. Therapeutic plasma exchange in nephrology. Where it applies? *Transfus Apher Sci*. 2019;58(3):262-265.
10. Kaplan AA. Therapeutic plasma exchange: a technical and operational review. *J Clin Apher*. 2013;28:3-10.
11. Bambauer R, Latza R, Burgard D, Schiel R. Therapeutic apheresis in hematologic, autoimmune and dermatologic diseases with immunologic origin. *Ther Apher Dial*. 2016;20(5):433-452.
12. Sesarman A, Vidarsson G, Sitaru C. The neonatal Fc receptor as therapeutic target in IgG mediated autoimmune diseases. *Cell Mol Life Sci*. 2010;67(15):2533-2550.
13. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol*. 2007;7:715-725.
14. Low SC, Mezo AR. Inhibitors of the FcRn:IgG protein-protein interaction. *AAPS J*. 2009;11(3):432-434.
15. Wang Y, Tian Z, Thirumalai D, Zhang X. Neonatal Fc Receptor (FcRn): a novel target for therapeutic antibodies and antibody engineering. *J Drug Target*. 2014;22(4):269-278.
16. Sockolosky JT, Szoka FC. The neonatal Fc receptor, FcRn, as a target for drug delivery and therapy. *Adv Drug Deliv Rev*. 2015;91:109-124.
17. Martins JP, Kennedy PJ, Santos HA, Barrias C, Sarmento B. A comprehensive review of the neonatal Fc receptor and its application in drug delivery. *Pharmacol Ther*. 2016;161:22-39.
18. Ward ES, Ober RJ. Targeting FcRn to generate antibody-based therapeutics. *Trends Pharmacol Sci*. 2018;39(10):892-904.
19. Zuercher AW, Spirig R, Baz Morelli A, Rowe T, Käsermann F. Next-generation Fc receptor-targeting biologics for autoimmune diseases. *Autoimmun Rev*. 2019;18(10):102366.
20. Biopharmaceutical Research Center, HanAll BioPharma Co., Ltd. HL161, a Novel Anti-FcRn Antibody as a New Therapeutic Option for Pathogenic IgG- Mediated Autoimmune Diseases. In: 2015 Protein and Antibody Engineering Summit.
21. Collins J, Jones L, Snyder M, et al. A novel anti-FcRn monoclonal antibody, is well tolerated in healthy subjects and reduces plasma IgG following subcutaneous or intravenous administration. In: 2019 American Academy of Neurology Annual Meeting. Philadelphia, PA; 2019.
22. See SB, Aubert O, Loupy A, et al. Post-transplant natural antibodies associate with kidney allograft injury and reduced long-term survival. *J Am Soc Nephrol*. 2018;29(6):1761-1770.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Yap DY, Hai J, Lee PC, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of HBM9161, a novel FcRn inhibitor, in a phase I study for healthy Chinese volunteers. *Clin Transl Sci*. 2021;14:1769–1779. https://doi.org/10.1111/cts.13019