Synopsis of Clinical Study Protocol

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Study No.: 9161.4

Protocol:

A randomized, double-blind, placebo-controlled, operationally seamless phase 2/3 clinical study to evaluate the efficacy and safety of HBM9161 weekly subcutaneous injection in patients with primary immune thrombocytopenia

Phase: Operationally seamless Phase 2/3

Country and study center: China, multicenter

Rationale:

The onset of primary immune thrombocytopenia is thought to be caused by increased platelet destruction and decreased platelet production due to anti-platelet antibodies. HBM9161 is a fully human anti-FcRn monoclonal antibody that can effectively remove pathogenic IgG, thereby relieving platelet destruction, and result in rapidly increasing platelet counts in patients. This study has an operationally seamless Phase 2/3 design, with a high dose (680 mg), a low dose (340 mg) of HBM9161, and a placebo group in the Phase 2 part. After the completion of Phase 2 part, an appropriate treatment dose will be selected to be further studied in the Phase 3 part, aiming to provide a new treatment option for the patients with primary ITP as early as possible.

Study Objectives:

Phase 2: Dose Selection and Efficacy Evaluation	
Study Objectives:	**Study Endpoints:**
Primary Objectives - To evaluate the early efficacy of weekly subcutaneous HBM9161 340 mg and 680 mg treatment in patients with primary immune thrombocytopenia (ITP) to make a go/no go decision for the phase 3 part and select a dose to be further	**Primary Endpoints** • Proportion of subjects who achieve a response (R) during the period from Week 1 to Week 7.

studied in the phase 3 part, the the phase 3 part decision is go.	
Secondary Objectives - To assess the efficacy of weekly subcutaneous HBM9161 340 mg and 680 mg in patients with primary immune thrombocytopenia (ITP).	**Secondary Endpoints** • Proportion of subjects whose platelet count is ≥ 30 × 10^9/L and at least 2 times of baseline at 4 or more visits out of the 6 visits in the period of Week 19 through Week 24, and who had no bleeding events and no rescue treatment prior to those platelet counts • Proportion of subjects who achieve response (R) within 24 weeks • Proportion of subjects who achieve complete response (CR) within 7 weeks • Proportion of subjects who achieve complete response (CR) within 24 weeks • Proportion of subjects who achieve platelet count ≥ 50 × 10^9/L at least 2 times within 7 weeks • Proportion of subjects who achieve platelet counts ≥ 50 × 10^9/L at least 2 times within 24 weeks • Time to Response: time from imitation of treatment to first response (R) or complete response (CR) • Duration of response: time from response (R) or complete response (CR) to first unmet response (R) or complete response (CR) Note: - Reaction (R) is defined as: Platelet counts ≥ 30 × 10 ^{9}/L and at least 2 times of baseline, confirmed by 2 tests (at least 7 days apart) , and no prior bleeding events and no rescue treatment. - Complete response (CR) is defined as: platelet counts ≥ 100 × 10 ^{9}/L should be achieved and confirmed in at least 2 tests (at least 7 days apart) without prior bleeding events and no rescue treatment.

Safety Objective - To assess the safety of weekly subcutaneous HBM9161 340 mg and 680 mg in ITP patients	**Safety Endpoints** • Severity and incidence of adverse events during 24 Weeks
Exploratory Objectives - Other efficacy assessments - Biomarker assessments - Immunogenicity of HBM9161 - Exploratory characteristics of the pharmacokinetics (PK) of HBM9161 in patients with primary immune thrombocytopenia based on population pharmacokinetic (PopPK) analysis - To assess the relationship between HBM9161 exposure and efficacy and adverse events	**Exploratory Endpoints** • WHO bleeding score of subjects from baseline to Week 24 • Change in platelet count over 24 weeks compared to baseline • Proportion of subjects with a decrease in ITP concomitant medication over 24 weeks compared to baseline • Proportion of subjects treated with rescue therapy within 24 weeks compared to baseline • Change in serum IgG, IgM, IgA, albumin levels from baseline to Week 24 • Anti-platelet autoantibodies: to assess changes compared to baseline of anti-GPIIb/IIIa, anti-GPIb/IX, and anti-GPIa/IIa antibodies. • Anti-drug antibodies: to assess changes in serum anti-HBM9161 antibodies compared to predose. • Pharmacokinetics evaluation: all data of HBM9161 plasma concentration obtained in this study will be used for the PopPK analysis, which is to establish a PK model to characterize the PK of subcutaneous injection of HBM9161. • Dose-response assessment: to explore the correlation between PK/efficacy and PK/safety.
Phase 3: Efficacy and Safety Assessment	
Primary Objectives - To evaluate the efficacy of weekly subcutaneous HBM9161 (dose to be determined) in patients with primary immune thrombocytopenia (ITP)	**Primary Endpoints** • Proportion of subjects with ≥ 4 visits with platelet counts ≥ 30×10^{9}/L and at least 2 times higher than baseline and no bleeding events and no rescue treatment in 6 visits from Week 19 to Week 24.

	Note: The primary endpoint of Phase 3 may be reasonably changed based on the data available in Phase 2 to more accurately reflect the long-term efficacy of the product.
Secondary Objectives - To assess the other efficacy assessments of weekly subcutaneous HBM9161 (dose to be determined) in patients with primary immune thrombocytopenia (ITP)	**Secondary Endpoints** • Proportion of subjects who achieve response (CR) within 7 weeks • Proportion of subjects who achieve response (R) within 24 weeks • Proportion of subjects who achieve complete response (CR) within 7 weeks • Proportion of subjects who achieve complete response (CR) within 24 weeks • Proportion of subjects who achieve platelet count ≥ 50 × 10^9/L at least 2 times within 7 weeks • Proportion of subjects who achieve at least 2 platelet counts ≥ 50 × 10^9 /L within 24 weeks • Time to Response: time from initiation of treatment to first response (R) or complete response (CR) • Duration of response: time from response (R) or complete response (CR) to first unmet response (R) or complete response (CR)
Safety Objective - To assess the safety of weekly subcutaneous HBM9161 (dose to be determined) in patients with primary immune thrombocytopenia (ITP)	**Safety Endpoints** • Severity and incidence of adverse events during 24 weeks
Exploratory Objectives - Other efficacy assessments - Biomarker assessments - Immunogenicity of HBM9161 - Exploratory characterization of the PK of HBM9161 in patients with primary immune thrombocytopenia based on the PopPK assay, as needed	**Exploratory Endpoints** • WHO bleeding score of subjects from baseline to Week 24 • Change in platelet count over 24 weeks compared to baseline

- To assess the relationship between HBM9161 exposure and efficacy and adverse events as needed.	• Proportion of subjects with a decrease in ITP concomitant medication over 24 weeks compared to baseline • Proportion of subjects treated with rescue therapy within 24 weeks compared to baseline • Change in serum IgG, IgM, IgA, albumin levels from baseline to week 24 • Platelet autoantibodies: to assess changes compared to baseline of anti-GPIIb/IIIa, anti-GPIb/IX, and anti-GPIa/IIa antibodies • Anti-drug antibodies: to assess changes in serum anti-HBM9161 antibodies compared to predose. • Pharmacokinetics evaluation: all data of HBM9161 plasma concentration obtained in this study will be used for the PopPK analysis, which is to establish a PK model to characterize the PK of subcutaneous injection of HBM9161. • Dose-response assessment: To explore the correlation between PK/efficacy and PK/safety.

Study Design:

A randomized, double-blind, placebo-controlled; Phase 2/3 operational seamless design

Study Population:

Phase 2 part: 36 patients (12 in Group 1, Group 2 and placebo group respectively) are planned to be randomized. If any subject drops out within 7 weeks after the first dose (including Visit 9), the same number of subjects will be enrolled to replace those who has dropped out (up to 6 subjects). The actual group will be assigned and balanced by randomization system..

Phase 3 part: 230 subjects (115 subjects each in the treatment and placebo groups) are planned to be randomized. The sample size may be increased according to the phase 2 part results, but the final sample size will not exceed 400.

Main Inclusion and Exclusion Criteria (for both phase 2 and phase 3 parts):

Inclusion Criteria:

1. Signed written informed consent.
2. ≥ 18 years of age at the screening visit, male or female.

3. Female patients will be eligible to participate if meeting the criteria below:

a. Non-childbearing potential (i.e., physiologically incapable of pregnancy, including women who have been menopausal for 2 years)

b. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at the first visit , and agreed to correctly use one of the following acceptable and effective methods of contraception (i.e., following the approved product label and physician's instructions) throughout the study from the start of study visit (Screening) until 90 days after the last dose:

- Complete abstinence (when consistent with the patient's preference and previous lifestyle); or
- Levonorgestrel implant should be implanted at least 1 month ahead of study drug administration, but implant time cannot be more than 3 years; or
- Progesterone should be injected at least 1 month ahead of that study drug administration; or
- Oral birth control pills (combination contraceptives or progestins only) administered for at least 1 month prior to study drug administration; or
- Dual birth control: condom or cervical cap (diaphragm or cervical cap) with spermicide (foam/gel/cream/suppository); or
- Intra-uterine devices (published data showing an estimated maximum failure rate is less than 1% per year), implanted by qualified physicians; or
- Estrogen vaginal ring; or
- Transcutaneous contraceptive patch.

4. Male patients must use effective contraception methods or their heterosexual partners must use effective birth control during their participation in this clinical trial.
5. Diagnosis criteria: meet the American Society of Hematology 2011 diagnosis criteria for persistent or chronic ITP. The average number for platelet count at the screening visit and predose platelet count on the day of first dose (at least 1 day apart) is $< 30 \times 10^9$/L, and platelet count is not $> 35 \times 10^9$/L for any of two tests. No severe bleeding occurs within 4 weeks prior to the screening visit.
6. Patients who have received and failed (poor response, or unmaintained response, or relapse) at least 1 first line of ITP therapy (glucocorticoids and/or intravenous gamma globulin), or who are contraindicated, intolerable, or refuse standard therapy.
7. This study allows concomitant drugs for the treatment of ITP, detailed requirements are as follows:

- Glucocorticoids: prednisone or other equivalents $\leq$ 20 mg/day are allowed within at least 2 weeks prior to the first dose of the study drug, with dose unchanged or regularly reduced;
- Danazol: The dose remained unchanged within 3 months prior to the first dose of study drug or has been discontinued for at least 2 weeks prior to the first dose of study drug;
- Immunosuppressants (azathioprine, cyclosporine A, mycophenolate mofetil only): The dose remains unchanged within 3 months prior to the first dose of the

study drug, or has been discontinued for at least 2 weeks prior to the first dose of the study drug;

- Eltrombopag: The dose remained unchanged within 4 weeks prior to the first dose of the study drug or has been discontinued for at least 2 weeks prior to the first dose of the study drug.

8. Willing and be able to receive treatment and complete appropriate assessments as required by the protocol, at the discretion of the investigator.
9. Clinical laboratory results at screening must be acceptable to the investigator.

Exclusion criteria:

1. The patient has severe ITP condition at screening, inappropriate for participation in the study as judged by the investigator (e.g., life-threatening platelets decrease, major bleeding events or symptoms or signs suggestive of potential major bleeding events, and requirement of rescue treatment, including intravenous gamma globulin, anti-D immunoglobulin, high-dose glucocorticoid, or plasmapheresis, etc.).
2. Has a history of serious allergic disease or known sensitivity to any components of the study drug.
3. Other autoimmune systemic diseases beyond ITP.
4. Multi-lineage immune cytopenia, such as Evan's syndrome, autoimmune pancytopenia.
5. Secondary ITP caused by leukemia; lymphoma; lymphoproliferative disorders; multiple myeloma; drugs (e.g., quinine, heparin); thyroid disease; cirrhosis; HIV infection; hepatitis C; and antiphospholipid antibody syndrome, etc.
6. Has received a vaccine within 4 weeks prior to the first dose of the study drug or is scheduled to receive a vaccine during the study.
7. Takes anticoagulants or any agents that have antiplatelet effect or can affect thrombopoiesis within 3 weeks prior to the first dose of the study drug.
8. Has received transfusion of blood (including platelet transfusion) within 1 week prior to the first dose of the study drug.
9. Has received the intravenous gamma globulin, anti-D immunoglobulin, or plasmapheresis within 2 weeks prior to the first dose of the study drug.
10. Has received high-dose dexamethasone or high-dose methylprednisolone within 2 weeks prior to the first dose of the study drug.
11. Has received recombinant human thrombopoietin (rhTPO) within 4 weeks prior to the first does of the study drug.
12. Has received romiplostim within 4 weeks prior to first dose of the study drug.
13. Has received splenic tyrosine kinase inhibitors (Syc inhibitors such as fostamatinib) within 4 weeks prior to the first dose of the study drug.
14. Has received rituximab or other non-rituximab anti-CD20 drugs within 6 months prior to the first does of the study drug.
15. Has been treated with splenectomy within 4 weeks prior to first dose of the study drug.

16. Has received biotherapeutic or investigational drugs not mentioned above within 3 months or 5 half-lives of drugs, whichever is longer, prior to the first dose of the study drug.
17. Any thromboembolic or embolic events within 12 months prior to the first does of the study drug.
18. Plans to take surgery during the study.
19. Active infection at the screening visit, or a serious infection (requiring intravenous antimicrobial therapy or hospitalization) within 8 weeks prior to the first dose of the study drug, or any infection requiring oral antibiotics within 2 weeks prior to the first dose of the study drug, or has symptoms due to fever or viral, bacterial (including upper respiratory tract infection), fungal (non-skin sites), or other infection within 1 week before the first dose of the study drug, previous or current human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection and current hepatitis B virus (HBV) infection. Patients to be enrolled at the screening visit must have negative results for the tests below: HBV surface antigen, HCV antibody, HIV antibody. Patients with negative HBV surface antigen but positive core antibody should be tested HBV-DNA, and patients with clinical significantly HBV-DNA increase should be excluded.
20. Has tuberculosis (TB) infection; with a high risk of TB infection; latent TB infection; or a history of TB infection should be excluded. Other patients are required to receive tuberculin test or interferon-gamma release test to rule out active TB infection.
21. Serum total IgG < 700 mg/dL at the screening visit.
22. Severe anemia (hemoglobin < 90 g/L), leukopenia (white blood cell count < 3 x 10^9/L), neutropenia (absolute neutrophil count < 1.5 x 10^9/L), or coagulation dysfunction (international normalized ratio[INR] > 1.5 or activated partial thromboplastin time [aPTT] > 1.5 times the upper limit of normal range).
23. Hepatic insufficiency with one or more of the following criteria met:
    a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 times the upper limit of normal range at the screening visit;
    b. Total bilirubin > 1.5 times the upper limit of normal range at the screening visit;
    c. Severe cirrhosis (Child-Pugh grade C).
24. Creatinine clearance ≤ 50 ml/min (calculated by the Cockcroft Gault formula) at the screening visit.
25. Uncontrolled hypertension, i.e., blood pressure is still higher than 160/100 mmHg after appropriate treatment.
26. Severe cardiovascular (including arrhythmias increasing the risk of embolism at discretion of the investigator, such as atrial fibrillation), liver, kidney, respiratory, or hematological disorders, or other medical or mental illness considered to prevent the patients from participating in the study.
27. History of malignant tumor, unless cured with appropriate treatment and no relapse for more than 3 years before the first dose of the study drug. Non-melanoma skin cancer in situ that has been completely resected by surgery (e.g., basal cell carcinoma or squamous cell carcinoma) or cervical cancer in situ can be enrolled.

28. Pregnant or lactating patients; or those who are going to become pregnant during the study.
29. Patients who are alcohol or drug dependence/abuse at present or during the past 1 year, except for nicotine and coffee.
30. The investigator/study center personnel directly related to the study, or an immediate relative of the investigator/study center personnel ("immediate family member" means a spouse, parent, child, or sibling [whether biological or legal adoptive relationship]).

Study Drug:

Phase 2 part: HBM9161

-Dose: Group 1: 340 mg; Group 2: 680 mg

- Method and route(s) of administration: The drug will be administered by subcutaneous injection once a week and 4 times per cycle. The number of treatment cycles will be as clinically indicated, with no more than 3 cycles per subject in the overall trial.

Phase 3 part: HBM9161

- Dose: to be determined (based on data from phase 2 part)

- Method and route(s) of administration: The drug will be administered by subcutaneous injection once a week, 4 times per cycle. The number of treatment cycles will be as clinically indicated, with no more than 3 cycles per subject in the overall trial.

Rescue treatment:

- Rescue treatment will be allowed during this study, including an increase in the dose or frequency of existing ITP concomitant drugs, and the addition of intravenous gamma globulin, anti-D immunoglobulin, high-dose glucocorticoid pulse, recombinant human thrombopoietin (rhTPO) or thrombopoietin receptor agonists, vinblastine, platelet transfusion, and plasmapheresis. The use of rescue treatment is based on the investigator's medical judgement and can be referred to the Expert Consensus on the Diagnosis and Treatment of Primary Immune Thrombocytopenia in Adults (2016 Edition), e.g., life-threatening thrombocytopenia, major bleeding events (WHO Bleeding Score Grade 3 or 4) or the presence of symptoms or signs suggestive of potential bleeding, and should be confirmed by the sponsor. Patients who achieve a response (R) after receiving rescue treatment should be considered nonresponsive when calculated the response rate.

Control Drug:

Placebo

- Dose: Not applicable

- Method and route(s) of administration: The drug will be administered by subcutaneous injection once a week and 4 times per cycle, with no more than 3 cycles per subject in the overall trial.

Treatment Duration (for both phase 2 and phase 3 parts):

3 weeks, once a week, 4 doses.

If subjects who had a response (R) or complete response (CR) to study drug in the previous cycle during the 21-week follow-up period had relapse (platelets < 30 ×10 ^{9}/L confirmed in 2 tests at least 1 day apart). Additional treatment cycle of study drug may be arranged once investigators considered as subjects were not indicated for rescue treatment and this should be confirmed by the sponsor. The treatment of the additional cycles continues with the original double-blind treatment, and the drugs are given once weekly for 4 weeks. The interval between the first dose of the additional cycles and the last dose of the previous cycle must be at least 4 weeks. The total number of the treatment cycles for subjects should not exceed 3, i.e. the total number of doses should not exceed 12.

Study Duration (for both phase 2 and phase 3 parts):

26 weeks in total (2-week screening + 3-week treatment + 21-week follow-up).

During the 21-week follow-up period, for subjects who receive additional treatment cycles, the subsequent visits after the first dose of additional cycles should be performed same as the visits from Day 0 (Visit 2) as specified in the study schedule. Except for randomization, all the procedures should be done. However, assessments to be performed should accord toVisit 20 in the study schedule. If the Week 24 visit is less than 5 weeks from the last dose of study drug, or the last treatment cycle has not been completed at the Week 24 visit, the follow-up period will be extended up to 5 weeks after the last study dose. For those subjects with extended follow-up period, the last visit assessments will also be performed as according to Visit 20 in the study schedule (see Flow Chart of Additional Treatment Cycles).

Statistical Analysis:

The primary endpoint in the phase 2 part is the proportion of subjects who achieve a response (R) between the Week 1 and Week 7. Based on data observed in this study and external information available, the sponsor will make following decisions based on the totality of information at the interim analysis at the end of Week 7 in the phase 2 part:

- whether to proceed to the phase 3 part;
- select a dose to befurther studied in the phase 3 part.

Whether to proceed to the phase 3 part will be based on the Go/No-Go decision framework. If at least one dose shows a high likelihood that the target efficacy can be achieved and the safety of this dose is acceptable, the phase 3 part will start. On the other hand, if the efficacy of both doses is shown to be unlikely to be clinically significant, the trial will be terminated and Phase 3 will not be initiated. If the analysis results do not meet any of the two situations above, the subjects will continue to be observed or sample size will be increased to collect more long-term efficacy data to decide whether to enter Phase 3. The dose selection for the Phase 3 will be based on the comparisons of the efficacy, safety and biomarkers between the two doses.

The primary efficacy endpoint in the Phase 2 is set primarily to verify the mechanism of action of the drug. Since the primary efficacy endpoint in the Phase 2 is for short-term efficacy assessment and the primary efficacy endpoint in the Phase 3 is for long-term efficacy assessment, the decision for Phase 3 will consider not only the observed short-term efficacy as measured by the Phase 2 primary efficacy endpoint, but also the long-term efficacy observed in subjects who have partially completed the trial, the predictions of

the long-term efficacy and the duration of efficacy based on the biomarkers, the efficacy and safety of the competitive products, and the safety data observed from this trial.

The primary endpoint of the Phase 3 is the proportion of subjects with a platelet count ≥ 30 × 10^9/L at ≥ 4 of 6 visits from Week 19 to 24 and the platelet count is at least twice baseline level, without bleeding events or rescue treatment. The statistical tests for differences in response rates between groups will be performed based on a normal approximation of the binomial distribution without continuity correction.

The hierarchical testing will be used to analyze the secondary endpoints in the Phase 3 trial. If the statistical test of the primary efficacy endpoint is statistically significant, other efficacy measures between the treatment groups will continue to be tested. The secondary endpoints will be ranked tentatively as the response rate within 7 weeks, the response rate within 24 weeks, the complete response (CR) rate within 24 weeks, and the complete response (CR) rate within 7 weeks.

An independent data monitoring committee (DMC) will be established prior to the enrollment of the first subject to periodically review the safety data for ensuring the safety of the subjects. The data monitoring committee will be responsible for the planned interim analysis, interpretation of the results, and the recommendations for action according to the protocol. To ensure the credibility of the trial, the sponsor will not be involved in the operation of this independent data monitoring committee. The persons involved in the trial, including all the sponsor employees, and the third-party personnel and investigators related to the trial, cannot be the members of the data monitoring committee.

Population Pharmacokinetics and Dose-Response Analysis:

All HBM9161 plasma concentration data obtained in this study will be used for the PopPK analysis (using a nonlinear mixed effects modeling [NONMEM]) to establish a PK model to characterize the PK of subcutaneous injection of HBM9161. The individual subject exposure parameters will be estimated based on the parameters estimated by the final PK model established for the further dose-response (exposure-response) analyses, including the exploratory analysis of correlation of PK/efficacy and PK/safety. The results of these analyses will be reported separately.

STUDY SCHEDULE

Study Phase	Screening Phase	Treatment Phase				Follow-up Phase[l]															Early Withdrawal Visit[b]
Visit Number																					ET
Weeks																					
Days																					
Visit Window (days)																					
Informed Consent																					
Demographic Information																					
Disease and Treatment History																					
Concomitant Treatment Collection																					
Vital Signs (temperature, blood pressure, pulse)																					
Complete Physical Examination																					
Key Physical Examination																					
12-lead Electrocardiogram		X[m]																			
Hematology																					
Blood Biochemistry		X[m]																			
Coagulation																					
Viral Serology																					
Hepatitis B Virus DNA[e]		X[m]																			
Mycobacterium Tuberculosis Test[f]																					
Urine Analysis		X[m]																			
Serum Globulin, Albumin		X[m]																			
Pregnancy Test[g]																					

(continued)

Study Phase	Screening Phase	Treatment Phase				Follow-up Phase[l]															Early Withdrawal Visit[b]
Visit Number																					ET
Weeks																					
Days																					
Visit Window (days)																					
Review of Inclusion/Exclusion Criteria																					
Subject Randomization																					
Study Drug Administration																					
Injection Site Assessment																					X[b]
Dispensing/Return of Subject Diary[h]																					
Review of Subject Diary																					
Adverse Event Collection																					
WHO Bleeding Score																					
Anti-HBM9161 Antibody Test[i]																					
Immunoglobulins (IgG, IgM, IgA)																					
Platelet Autoantibodies[j]																					
PK Blood Sample Collection[k]																					

Note:

a. Date of first dose of HBM9161 injection.

b. If the subject withdraws from the study early, the withdrawal visit should be completed within 2 days of the decision to withdraw from the study; if the subject withdraws in the middle of the treatment period, please observe the injection site reaction at the withdrawal visit until the reaction disappears.

c. The complete physical examination should be performed at the Screening Visit, Visit 6 (Week 4), Visit 9 (Week 7), Visit 20 (Week 24), and the Early Withdrawal Visit (Includes cardiovascular, respiratory, gastrointestinal, skin, neurological, and musculoskeletal systems, as well as head, eyes, ears, mouth, nose, throat, neck, lymph nodes and edema). Height and weight will be measured and recorded at the screening visit. Key physical examinations (including skin, mucosa and organ hemorrhage and edema) may be performed at other visits.

d. Viral serology test should be performed at screening, including HIV, HBsAg, HBcAb and HCV antibody. The HBV-DNA testing should also be performed in the subjects with HBsAg-negative but HBcAb-positive, and the subjects with clinically significant elevations in HBV-DNA are excluded.

e. The HBV-DNA testing is only performed in the subjects with HBsAg negative but HBcAb positive. The subjects with clinically significant elevations in HBV-DNA should be considered for the addition of the anti-HBV drugs according to the relevant guidelines.

f. The subjects with the known tuberculosis infection, a high risk of tuberculosis infection, latent tuberculosis infection or a history of tuberculosis infection should be excluded. Other subjects should have a tuberculin test or interferon gamma release assay to rule out the active TB infection.

g. All the female subjects of childbearing potential should complete the blood human chorionic gonadotropin (HCG) pregnancy test at screening. The serum or urine pregnancy tests may be done at the subsequent visits.

h. The subject diary helps the subjects record the medications and the adverse event across the visits.

i. The ADA analysis will be performed under the control of the sponsor. The serum samples will be tested for anti-HBM 9161 antibodies using the currently approved bioanalytical methods. The raw data will be stored at the bioanalytical site. If the anti-HBM 9161 antibodies can be detected, the ADA titers will be further tested and further characterized using the validated cell-based NAb assays, if necessary, based on the ADA positive rate and titers.

j. Platelet autoantibodies, including anti-GPIIb/IIIa, anti-GPIb/IX and anti-GPIa/IIa antibodies, will be detected by the monoclonal antibody-specific immobilization of platelet antigen (MAIPA) or enzyme-linked immunosorbent assay (ELISA) methods. From the start of the first dose of the additional cycles, the subsequent sampling will be performed according to the blood collection schedule from Day 0 (Visit 2) on the study schedule.

k. The PK blood sample collection will be flexible and should be taken only within the time window. The blood samples will be collected within 2 h before dosing on Days 0, 7, 14 and 21, as close as possible to the time of dosing. The PK sampling can still be performed if the subject has taken the study drug before the blood collection, and the actual time of administration, dose and blood collection time need to be accurately recorded. The samples should be collected at site for follow-up visits on Day 28, 35 and 49, and the blood collection time needs to be accurately recorded. When an event of special interest (e.g., serious adverse event, etc.) occurs on and before Day 49, the investigator may choose to collect an unscheduled PK sample for the exploratory dose-response analysis, when available. If the subject withdraws from the study on or before Day 49, a PK sample may also be collected for the exploratory dose-response analysis. The PK blood samples may be collected as described above for subjects who receive the additional treatment cycles.

l. During the 21-week follow-up period, for the subjects who receive additional treatment cycles, the subsequent visits after the first dose of additional cycles should be performed same as the visits from Day 0 (Visit 2) as specified in the study schedule. Except for randomization, all the procedures will be consistent. However, the visit assessments will be performed same as with Visit 20 in the study schedule. If the Week 24 visit is less than 5 weeks from the last dose of study drug, or the last treatment cycle has not been completed at the Week 24 visit, the follow-up period will be extended to 5 weeks after the last study dose. For the subjects with extended follow-up period, the last visit assessments will also be performed same as Visit 20 in the study schedule (see Flow Chart of Additional Treatment Cycles).

m. If the assessment has been performed within ≤ 7 days before, it may not be performed at that visit day.

FLOW CHART OF ADDITIONAL TREATMENT CYCLES

Study Phase	Screening Phase	Treatment Phase				Follow-up phase																					Adjustment Visits Caused by Additional Cycles							
Visit Number																																		
Weeks																																		
Days																																		
Visit Window (days)																																		
Visit Number for the Same Process																																		
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m.Initiation of the additional cycles per protocol requirements