CLINICAL STUDY PROTOCOL SYNOPSIS

Company name: Harbour BioMed (Suzhou) Co., Ltd.

Address: Unit 202, A3 Building, No. 218 Xinghu Street, Suzhou Industrial Park, Suzhou

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Study No. 9161.3

Study Title:

A multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy, safety, pharmacodynamics and pharmacokinetics of HBM9161 (HL161) subcutaneous injection in patients with generalized myasthenia gravis

Clinical Phase: 2

Study Rationale:

Myasthenia gravis (MG) is an acquired autoimmune disease mediated by autoantibodies, like acetylcholine receptor antibody or muscle tyrosine kinase antibody. Pathological lesions mainly involve with the postsynaptic membrane of the neuromuscular junction, causing impaired transmission at the neuromuscular junction and weakness of skeletal muscle contraction, and even involve with respiratory muscles leading to crisis. Current main treatments for MG include cholinesterase inhibitors and glucocorticoids and other immunosuppressive drugs, but the efficacy and safety cannot meet the clinical needs of many patients. Plasmapheresis can rapidly remove pathogenic components such as antibodies from the blood, and is indeed effective in clinical practice and research reports, which is commonly used in patients with acute advanced disease, myasthenic crisis, and preoperative and perioperative management of thymectomy; however, its clinical application is limited because of its need for hospitalization, difficulty in operation, invasiveness and poor accessibility.

The mechanism of HBM9161 is to accelerate the clearance of pathogenic antibodies in vivo by blocking the human neonatal Fc receptor (FcRn); its good safety and pharmacodynamic (PD) effects to reduce immunoglobulin G (IgG) have been well documented in previous nonclinical and clinical studies; it is expected to reduce the levels of autoantibodies in MG patients to treat MG. Phase 2 clinical trials in MG of efgartigimod and rozanolixizumab, two FcRn inhibitors abroad with similar mechanisms, have been completed with positive clinical efficacy data and good safety, and phase 3 studies are currently in process. Based on the pathological characteristics of MG, mechanism of action of the study drug and data of similar products, HBM9161 is expected to provide clinical benefits for MG patients.

Study Objectives:

Primary study objective:

- To preliminarily evaluate the efficacy of HBM9161 subcutaneous injection in Chinese MG patients

Secondary study objectives:

- To evaluate the safety, PD and immunogenicity of HBM9161 subcutaneous injection in Chinese MG patients

Exploratory objectives:

- To characterize the pharmacokinetics (PK) profiles of HBM9161 in Chinese MG patients based on population pharmacokinetics (PopPK) analysis method
- To evaluate the relationship between HBM9161 exposure and PD/efficacy and adverse events (AEs), if data permit
- To evaluate the effect of HBM9161 treatment on complements

Study Endpoints:

Primary study endpoints:

- Change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score on Day 43

Secondary study endpoints:

Clinical response assessment:

- Change from Baseline in Myasthenia Gravis Composite Scale (MGC) Score on Day 43
- Change from baseline in Quantitative Myasthenia Gravis (QMG) score on Day 43
- Change from baseline in 15-item Myasthenia Gravis Quality of Life (MG-QoL15r) score on Day 43
- Percentage of patients with at least a 2-point reduction from baseline in the Myasthenia Gravis Activities of Daily Living (MG-ADL) score on Day 43
- Percentage of patients with improvement and exacerbation at Day 43 compared to baseline according to the Myasthenia Gravis Foundation of America post-intervention status (MGFA-PIS) classification:
    - Improvement: ≥ 3-point decrease in MGC score
    - Exacerbation: ≥ 3-point increase in MGC score
- Change in MG-ADL score from baseline to Day 120
- Change in MGC score from baseline to Day 120
- Change in QMG score from baseline to Day 120
- Change in MG-QoL15r score from baseline to Day 120

- Percentage of patients with sustained improvement from baseline to Day 120: an improvement (i.e., reduction) in MGC score of ≥ 3 points for consecutive 6 weeks
- Percentage of patients with sustained improvement from baseline to Day 120: an improvement (i.e., reduction) in MG-ADL score of ≥ 2 points for consecutive 6 weeks

Safety Assessments:

- Incidence of treatment-emergent AEs
- Change from baseline in albumin levels during the study

Pharmacodynamic Assessments:

- Changes in serum total IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4), immunoglobulin M (IgM), and immunoglobulin A (IgA) levels from baseline to Day 120
- Changes in serum acetylcholine receptor antibody (AchR-Ab) and muscle-specific tyrosine kinase antibody (MUSK-Ab) levels from baseline to Day 120

Immunogenicity:

- Change from pre-dose in serum anti-HBM9161 antibody and neutralizing antibody

Exploratory Endpoints:

- PopPK: All HBM9161 plasma concentration data obtained in this study will be used in the PopPK analysis to develop a PK model to characterize the PK profile of subcutaneous HBM9161
- Assessment of dose-response relationship: Correlation between PK/PD/efficacy [changes in serum AchR-Ab, MUSK-Ab, total IgG, and IgG subtypes levels and clinical benefit (MG-ADL, MGC, QMG, MG-QoL15r)] and PK/PD/safety will be explored if data permit
- Changes of serum complements (CH50, C3)

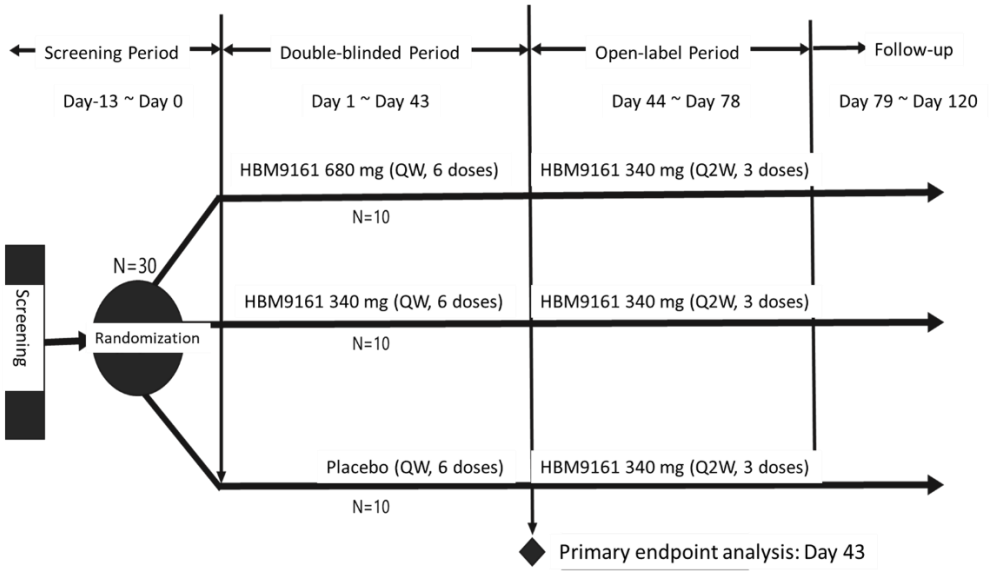
Study Design:

Randomized, double-blind, placebo-controlled, parallel. The study consists of a screening period, a double-blinded treatment period, an open-label treatment period, and a follow-up period.

Thirty subjects are planned to be randomized in a 1:1: 1 ratio to each of the three treatment groups, with 10 subjects in each group. Group 1 will receive HBM9161 680 mg (double-blind treatment period) + HBM9161 340 mg (open-label treatment period); Group 2 will receive HBM9161 340 mg (double-blind treatment period and open-label treatment period); and Group 3 will receive placebo (double-blind treatment period) + HBM9161 340 mg (open-label treatment period).

First, eligible subjects at screening will enter the double-blind treatment period and receive HBM9161 680 mg, HBM9161 340 mg, or placebo once weekly (QW) for a total of 6 doses under

blinded conditions; then all subjects will enter the open-label treatment period and receive HBM9161 340 mg once every 2 weeks (Q2W) for a total of 3 doses; after the end of dosing, they will enter the follow-up period and all subjects will be followed through Day 120.



During the study, blood samples for PK, PD, immunogenicity, and exploratory endpoints will be collected in accordance with the study schedule.

Study Population:

Patients with Myasthenia Gravis who are receiving stable treatments without being fully controlled, evaluated as Myasthenia Gravis Foundation of America (MGFA) clinical classification II A - IVa (incl. IIa, IIb, IIIa, IIIb and IVa type) and being serum AchR-Ab or MUSK - Ab positive.

Approximately 30 subjects are planned to be enrolled and randomized in a 1:1: 1 ratio to each of the three aforementioned treatment groups.

Main inclusion and exclusion criteria:

Inclusion Criteria:

1. Signed written informed consent form (ICF).
2. Male or female ⩾ 18 years of age at the screening visit.
3. Female subjects shall meet the following conditions to participate in this study:

a. Not of childbearing potential (ie, physiologically incapable of becoming pregnant, including women who have been postmenopausal for 2 or more years);

b. Of potential childbearing potential, have a negative serum pregnancy test result at the screening visit, and agree to adhere to one of the following acceptable effective methods of contraception (ie, per approved package inserts and physician instructions) consistently and correctly during the study, from the screening visit onwards until 14 days after the Final Visit:

- Total abstinence (based on subject preference and previous lifestyle); or
- Implantation of a levonorgestrel implant at least 1 month prior to study drug administration, but no longer than 3 years; or
- Injection of a progestogen at least 1 month prior to study drug administration; or
- A cycle of oral contraceptives (combined contraceptives or progestin-only) for at least 1 month prior to study drug administration; or
- Double contraception: condom or cervical cap (diaphragm or cervical cap) plus spermicide (foam/gel/cream/suppository); or
- An intrauterine device, implanted by a qualified physician; or
- Estrogen vaginal ring; or
- Contraceptive patch.

4. Male subjects shall use effective contraceptive methods or have their heterosexual partners use effective contraceptive methods during their participation in this clinical trial.

5. Meets MGFA myasthenia gravis clinical classification IIa-IVa (includes types IIa, IIb, IIIa, IIIb, and IVa) at the screening visit and at the baseline visit.

6. Positive AchR-Ab or MUSK-Ab at the screening Visit and meets at least 1 of the following 3 criteria:

a. Repeated electrical stimulation indicates neuromuscular junction transmission disorder (including history recording);

b. Positive Tensilon test or neostigmine test (including medical history record);

c. The patient's MG symptoms improve after treatment with oral cholinesterase inhibitors judged by physician.

7. MG-ADL score $\geqslant$ 6 points and eye muscle-related score less than 50% of the total score at screening visit and baseline visit.

8. Subjects on stable myasthenia gravis treatment at the randomization visit (Visit 2), and stable treatment is defined as follows:

a. Cholinesterase inhibitors: stable dose for more than 4 weeks at randomization visit; and suspension for more than 12 hours for all clinical assessments;

b. Corticosteroids: started at least 3 months prior to the randomization visit and at a stable dose for at least 1 month at the randomization visit;

c. Immunosuppressants:

- Azathioprine: initiated at least 12 months prior to the randomization visit and stable for at least 4 months at the randomization visit.

- Other immunosuppressive drugs (e.g., cyclophosphamide, cyclosporine A, tacrolimus, mofetil, methotrexate, etc.): started at least 6 months prior to the randomization visit and at a stable dose for at least 3 months at the randomization visit.

9. If taking a statin, a documented medical history is required to document that the dose and regimen were stable for 2 months prior to the Screening Visit.

10. Subject is willing and able to modify current disease therapy per protocol requirements at the discretion of the investigator.

11. Compliance: Subjects shall be willing to complete all visit assessments at the study site as required by the protocol.

12. Results from clinical laboratory tests at screening shall be acceptable to the investigator.

Exclusion Criteria:

1. Suffer from a significant disease or condition other than myasthenia gravis that, in the judgment of the investigator, would place the subject at risk for study participation or that would affect the results of the study and the subject's ability to participate in this study.

2. Females who are pregnant or lactating or planning to become pregnant during the study period, or females of childbearing potential who are not using an effective method of contraception.

3. Subjects with severe myasthenia gravis (such as Type IVb or V) who are judged by the investigator to be inappropriate for this study (e.g., expected to require artificial ventilation during the study).

4. Received thymectomy for less than 12 months at the screening visit or likely to require thymectomy during the study as judged by the investigator.

5. Received thymic radiation therapy less than 12 months at the screening visit or likely to require thymic radiation therapy during the study as judged by the investigator.

6. Subjects treated with intravenous gamma globulin, plasmapheresis or plasmapheresis, with the last completed treatment less than 4 weeks prior to the screening visit.

7. Received immunosuppressive monoclonal antibody therapy with last dose less than 6 months at screening visit, including but not limited to rituximab, bevacizumab, eculizumab, etc. If the end of rituximab or bevacizumab treatment has passed over 6 months, B cell counts are not returned to above the lower limit of normal range.

8. Splenectomized patients.

9. Presence of other autoimmune diseases (such as uncontrolled thyroid disease, severe rheumatoid arthritis, etc.) that may affect the efficacy assessment of the study drug or affect participation in this study.

10. Presence of other concurrent diseases or conditions that may affect the assessment of the efficacy of the study drug for the treatment of myasthenia gravis.

11. Have received a vaccine injection 4 weeks prior to the screening visit or are scheduled to receive a vaccine injection during the study.

12. Any active infection at the screening visit or serious infection requiring treatment with intravenous anti-infective drugs or hospitalization within 8 weeks before the screening visit.

13. Previous or current human immunodeficiency virus (HIV), hepatitis C virus (HCV) infection; subject has a positive test for any of the following at the screening visit: HCV antibody, HIV antibody type 1 and 2.

14. At the screening visit: the subject is positive for HBV surface antigen; the subject has negative HBV surface antigen and positive anti-HBV core antibody, and further test or medical documents within 12 weeks prior to screening visit confirms HBV-DNA quantitative detection > 2 000 IU/mL.

15. Previous or current infection with Mycobacterium tuberculosis (positive or indeterminate interferon gamma release test at 12 months prior to the screening visit).

16. Has acute liver injury (eg, hepatitis) or significant cirrhosis (Child-Pugh Class C) or any of the following:

a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 times the upper limit of normal (ULN) according to the laboratory reference range at the screening visit;

b. Total bilirubin > 1.5 times the upper limit of normal (ULN) at the screening visit according to the laboratory reference range.

17. Clinically significant laboratory abnormality that, in the opinion of the investigator, would pose a risk to the subject's participation in this study or interfere with study participation; or any of the following:

a. Total serum IgG at screening visit ≤ 6 g/L ;

b. Serum albumin < 3.5 g/dL at the screening visit;

c. Blood neutrophils < 1.5×10^9/L at the screening visit;

d. Blood calcium values more than 5% of the normal range.

18. Significant cardiovascular (including serious cardiac arrhythmias), hepatic, renal, respiratory, endocrine, or hematologic disease, or other medical or psychiatric condition that, in the opinion of the investigator, would preclude the subject from participating in the study or would require hospitalization during the study.

19. Malignancy at any time, including malignant thymoma, bone marrow or lymphodysplastic disease, etc.

20. Men with QTcF interval > 450 msec and women with > 470 msec (one retest is allowed to determine eligibility).

21. Alcohol or drug dependence/abuse at present or during past one year, except nicotine and coffee.

22. Subjects who are allergic to the trial drug or its components; or history of clinically significant allergic disease (including drug allergies, anaphylaxis) that, in the opinion of the investigator, affects the subject's participation in this study.

23. Patients who need to take prohibited drugs specified in the protocol during the screening period and treatment period of this clinical trial according to the investigator's judgment.

24. An investigator/site employee directly related to the study or an investigator/site employee directly related to the study is in an immediate family relationship ["immediate family"means a spouse, parent, child, or sibling (whether biological or legal)].

25. Subjects who were treated with an investigational drug in another clinical trial within the last 30 days or 5 half-lives or the time of effect of the drug, whichever was longer, prior to the screening visit (Note: Subjects who participated in an observational study, i.e., the study did not require a change in drug therapy or other intervention, were not excluded).

26. Subjects who have previously participated in clinical trials of drugs of the same class (FcRn inhibitors).

Study Drug:

Investigational Product: HBM9161 Injection

- Dose: 680 mg or 340 mg (depending on group assignment and study period)
- Method and route of administration: Subcutaneous injection, QW for the first 6 weeks, 6 doses in total; then Q2W for 3 doses in total.

Comparator: Placebo

- Dose: N/A
- Method and route of administration: Subcutaneous injection, QW for the first 6 weeks, 6 doses in total.

Study Duration:

Duration of participation for each patient is expected to be 19-20 weeks (1-2 weeks screening + 12 weeks treatment + 6 weeks follow-up)

STATISTICAL METHODS:

The primary objectives of this trial include the clinical verifying of the mechanism of action of the drug, providing the basis for entering the phase 3 trial, and supporting the dose selection and safety evaluation of the phase 3 trial. The primary efficacy endpoint is the improvement of MG-

ADL at Day 43 compared with the baseline. The sample size is selected based on the comprehensive consideration of the operability and the possibility of making the correct decision.

The statistical analysis of efficacy is divided into two steps: The efficacy of each dose relative to placebo will be first assessed separately, and a Phase 3 trial will be recommended if at least one of the doses shows a high likelihood of achieving the target efficacy with acceptable safety. If both doses are considered to have the potential to continue development, the efficacy of the two doses will be compared. If the efficacy of high dose (i.e., 680 mg) is significantly better than that of the low dose (i.e., 340 mg) with similar safety, it will be further evaluated in phase 3 trial, otherwise the low dose will be selected for the phase 3 trial.

Since this trial is exploratory, when about 15 subjects have completed double-blind medication and completed Visit 8 efficacy evaluation, an interim data review will be performed by the sponsor. According to the results of data review, the subject randomization process or sample size may be adjusted, including the premature termination of the trial. The specific analysis details and decision indicators are further described in the main body of the protocol and Statistical Analysis Plan (SAP). Given that the objectives of the trial are exploratory, no multiplicity adjustment will be made for this interim data review in the final analysis.

Population pharmacokinetics and dose-response analysis:

All HBM9161 plasma concentration data obtained in this study will be used in the PopPK analysis (using nonlinear mixed effects modeling [NONMEM]) if data permit, to develop a PK model to characterize the PK profiles of subcutaneous HBM9161. Individual exposure parameters for subjects will then be estimated based on established parameter estimates from the final PK model, which will be used for further dose-response (exposure-response) analyses, including PK/PD/efficacy and PK/PD/safety correlation exploratory analyses. Results of these analyses will be reported separately. The population PK/PD analysis after the end of this trial will try to provide a basis for dose selection in the phase 3 trial and determine the strategy for further trial implementation based on the analysis results.