Study Title:

A multicenter, randomized, double-blind, placebo-controlled, seamless and group sequential phase 2/3 study to evaluate the efficacy and safety of HBM9161 (HL161) subcutaneous injection in patients with generalized myasthenia gravis

Study No. 9161.3

Version No: .9.0/Date: July 21, 2021

CLINICAL STUDY PROTOCOL SYNOPSIS

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Study Title:

A multicenter, randomized, double-blind, placebo-controlled, seamless and group sequential phase 2/3 study to evaluate the efficacy and safety of HBM9161 (HL161) subcutaneous injection in patients with generalized myasthenia gravis

Clinical Phase: 2/3 seamless

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. Patients often have ocular muscle manifestations, and about 85% of patients will show symptoms other than ocular muscles and develop generalized myasthenia gravis (gMG). 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. At present, preliminary data have been obtained from the phase 2 clinical trial of HBM9161 in MG patients abroad, and positive clinical efficacy data and good safety and tolerability of HBM9161 in MG patients have been observed. At the same time, the phase 3 confirmatory study of the foreign FcRn inhibitor efgartigimod with similar mechanism has been completed. The main study results have confirmed the significant clinical efficacy and good safety of this target drug in MG patients. At present, this drug has been submitted for marketing application.. 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.

Since there is lack of effective treatment for myasthenia gravis, and the overseas MG phase 2 and phase 3 data of HBM9161 and the product with the same target have shown the efficacy and safety of FcRn target product in the treatment of myasthenia gravis, in order to accelerate the research and development progress of innovative drugs to meet the medical and patient needs as soon as possible, this study will adopt the operationally seamless phase 2/3 trial design to accelerate the connection between phase 2 and phase 3 subjects and improve the operation efficiency of the whole study, thereby accelerating the progress of clinical development.

Operationally seamless phase 2/3 trial design is a commonly used research and development strategy, and phase 2 data provides guidance for phase 3 trial, but the data of phase 2 and phase 3 are analyzed separately, so phase 2 study will not affect the integrity and effectiveness of phase 3 study.

Phase 2 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
- 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

Phase 3 study objectives:

Primary study objective:

- To verify the efficacy of HBM9161 subcutaneous injection in Chinese patients with gMG

Secondary study objectives:

- To further assess the safety, pharmacodynamics and immunogenicity of HBM9161 subcutaneous injection in Chinese patients with gMG
- The available PK and PD data for HBM9161 will be combined to develop a PopPK/PD model to further characterize the quantitative relationship between PK and/or

PD and efficacy and/or safety measures The impact of demographic characteristics, disease progression, and concomitant medications on PK and/or PD characteristics will be investigated systematically and quantitatively. The relationship between exposure to HBM9161, PD and efficacy/adverse events (AEs) will be further assessed as data permit.

Phase 2 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:

- Occurrence and time course of 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)

Phase 3 study endpoints:

Primary study endpoints:

- Percentage of patients with sustained improvement (AChR-Ab-positive or MuSK-Ab-positive patient population) during the first treatment period and observation period (baseline to Day 64): a reduction of ⩾ 3 points from the baseline of Myasthenia Gravis Activities of Daily Living Scale (MG-ADL) score that persists for at least 4 weeks

Secondary study endpoints:

Clinical response assessment:

- Percentage of patients with sustained improvement (i.e. Entire Population) during the first treatment period and observation period (Baseline to Day 64): a reduction of ≥ 3-point from the baseline of Myasthenia Gravis Activities of Daily Living Scale (MG-ADL) score that persists for at least 4 weeks
- Percentage of patients with sustained improvement (AChR-Ab-positive or MuSK-Ab-positive patient population) during the first treatment period and observation period (baseline to Day 64): a reduction of ⩾ 3 points from the baseline of Quantitative Myasthenia Gravis (QMG) score that persists for at least 4 weeks

- Percentage of the time that patients remain in clinical improvement: Percentage of the time that patients achieve clinical improvement (≥ 3 Point Reduction from Baseline for MG-ADL Score) from Baseline to Week 24 (AChR-Ab-positive or MuSK-Ab-positive Patient Population)
- Percentage of patients with minimal clinical manifestations (Minimal Symptom Manifestation, MSE) at any visit during the first treatment period and observation period (baseline to Day 64) (AChR-Ab positive or MuSK-Ab positive patient population): MG-ADL score of 0 or 1
- Percentage of patients with early improvement during the first cycle of treatment (AChR-Ab positive or MuSK-Ab positive patient population): a reduction of ⩾ 3-point of MG-ADL score at any visit from baseline to Day 15
- Percentage of patients with sustained improvement (AChR-Ab-positive or MuSK-Ab-positive patient populations) during the second treatment period and observation period: a reduction of ⩾ 3 points from the baseline of MG-ADL score that persisted for at least 4 weeks

Safety Assessments:

- Overall safety profile (adverse events, laboratory tests, vital signs, etc.) of HBM9161
- Change from baseline in albumin and LDL-C levels during the study

Pharmacodynamic Assessments:

- Change of baseline in serum total IgG, serum acetylcholine receptor antibody (AChR-Ab), and muscle specific tyrosine kinase antibody (MuSK-Ab), and change in serum complement (CH50, C3)

Immunogenicity Assessment:

- Occurrence and time course of serum anti-HBM9161 antibodies and neutralizing antibodies

Population pharmacokinetics analysis:

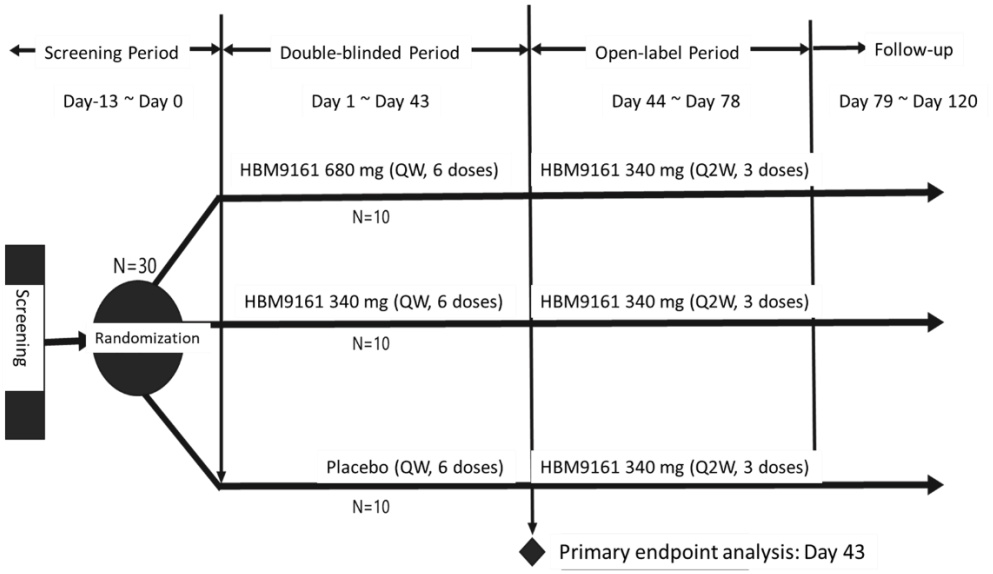
The available PK and PD data for HBM9161 will be combined to develop a PopPK/PD model to further characterize the quantitative relationship between PK and/or PD and efficacy and/or safety measures. The impact of demographic characteristics, disease progression, and concomitant medications on PK and/or PD will be investigated systematically and quantitatively. The relationship between exposure to HBM9161, PD and efficacy/adverse events (AEs) will be further assessed as data permit.

Phase 2 Study Design:

Randomized, double-blind, placebo-controlled, parallel. This phase 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. Subjects from Group 1 will receive HBM9161 680 mg (double-blind treatment period) + HBM9161 340 mg (open-label treatment period); those from Group 2 will receive HBM9161 340 mg (double-blind treatment period and open-label treatment period); and those from 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 this phase, blood samples for PK, PD, immunogenicity, and exploratory endpoints will be collected in accordance with the study schedule.

Phase 3 study design:

This phase is a randomized, double-blind, placebo-controlled, parallel-group, group sequential design. Trial procedures include screening period (2 weeks), first treatment period (6 weeks), observation period (4 weeks), individualized follow-up period (until the patient meets the criteria for re-treatment), second treatment period (6 weeks) , observation period (4 weeks) and follow-up period (to 5 weeks after last dose of study drug or to Week 24, which occurs later); the total length of the double-blind period will be at least 24 weeks up to 28 weeks. The latest start of

retreatment in this study phase will be Day 127 (Week 18). Subjects will be dosed for up to two treatment cycles throughout the study. Subjects who complete this study will have access to enter an open-label extension trial (separate protocol) to receive open-label HBM9161 Treatment.

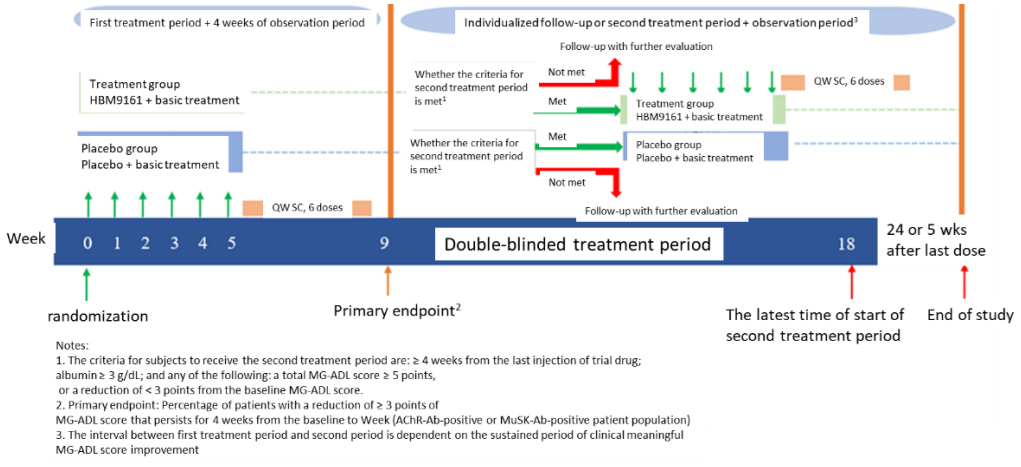
A total of 120 subjects with positive AChR-Ab or MuSK-Ab and up to 24 subjects with negative AChR-Ab and MuSK-Ab are planned for this phase (The randomizationwill end after approximately 120 subjects with positive serum AchR-Ab or MUSK-Ab are enrolled) and randomized into 2 treatment regimens in a 1:1 ratio. Arm 1 will receive HBM9161 680 mg; Arm 2 will receive placebo. Whether or not AChR-Ab or MuSK-Ab is positive, and whether or not concomitant steroids are used will be randomization stratification factors.

First, eligible subjects will be screened into the double-blind treatment phase and blindly assigned to receive either HBM9161 680 mg or placebo for the first treatment period, administered once weekly (QW) for 6 doses, followed by an observational follow-up of at least 4 weeks for the primary endpoint analysis on Day 64.

Subjects who complete the first treatment period will start the administration of the second treatment period if they meet the dosing criteria for the second treatment period at Week 9. Otherwise they will be followed individually until they require a second cycle of therapy or until Week 24.

The second treatment period will be administered once weekly (QW) for a total of 6 doses in the first treatment period, followed by an observation period (4 weeks) and a follow-up period (5 weeks after the last dose of study drug or until Week 24 (which occurs later). Subjects will be dosed for up to two treatment cycles during the study, with the start of the second treatment period no later than Day 127 (i.e. Week 18).

The criteria for subjects to receive the second treatment period are: ≥ 4 weeks from the last injection of trial drug; albumin ≥ 3 g/dL; and any of the following: a total MG-ADL score ≥ 5 points, or a reduction of < 3 points from the baseline MG-ADL score.



Notes:
1. The criteria for subjects to receive the second treatment period are: ≥ 4 weeks from the last injection of trial drug; albumin ≥ 3 g/dL; and any of the following: a total MG-ADL score ≥ 5 points, or a reduction of < 3 points from the baseline MG-ADL score.
2. Primary endpoint: Percentage of patients with a reduction of ≥ 3 points of MG-ADL score that persists for 4 weeks from the baseline to Week (AChR-Ab-positive or MuSK-Ab-positive patient population)
3. The interval between first treatment period and second period is dependent on the sustained period of clinical meaningful MG-ADL score improvement

During the study, blood samples for PK, PD, immunogenicity, etc. will be collected according to the study schedule.

Phase 2 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.

Phase 3 study population

Patients with Myasthenia gravis with American Myasthenia Gravis Association (MGFA) clinical classification IIa-IVa (including types IIa, IIb, IIIa, IIIb, and IVa) who are on stable therapy but whose condition is not fully controlled.

Approximately 144 subjects are planned, with 120 subjects positive for serum AchR-Ab or MUSK-Ab and up to 24 subjects negative for both serum AchR-Ab and MUSK-A (The study will end when 120 subjects positive for serum AchR-Ab or MUSK-Ab are enrolled), to be randomized in a 1:1 ratio to the 2 aforementioned treatment regimens.

Phase 2 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 3creterion:

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 at the discretion of the physician.

7. MG-ADL score ≥ 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 suspended for more than 12 hours when all clinical assessments are conducted;

b. Corticosteroids: start 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: start 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.): start 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 medical history is required to document that the dose and regimen have been 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 (e.g., 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, will not be excluded).

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

Phase 3 main inclusion and exclusion criteria:

1. Signed written informed consent form (ICF).
2. Male or female ≥ 18 years of age at the screening visit.
3. Female subjects must 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 product label insert 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 must 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 or negative AchR-Ab/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 medical history record);

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

c. The patient's MG symptoms improve after treatment with oral cholinesterase inhibitors at the judge of the physician.

7. MG-ADL score ≥ 5 and eye muscle-related score less than 50% of the total score at screening visit and baseline visit.

8. QMG score ≥ 11 at screening visit and baseline visit.

9. Subjects with stable treatment for myasthenia gravis at the randomization visit (Visit 2), where stable treatment is defined as follows (at least one is used):

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

b. Corticosteroids: start at least 3 months prior to randomization visit and stable for at least 1 month at randomization visit (The total daily dose of glucocorticoids should not exceed prednisone 4 0 mg or equivalent) ;

c. Immunosuppressants:

- Azathioprine: start 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.): start at least 6 months prior to the randomization visit and at a stable dose for at least 3 months at the randomization visit.

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

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

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

13. Results from clinical laboratory tests at screening must be acceptable to the investigator.

Exclusion Criteria:

1. Has a serious illness or condition other than myasthenia gravis that, in the judgment of the investigator, would put the subject at risk because of participation in the study, or that would affect the results of the study and the subject's ability to participate in the 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. Patient has a BMI $\geqslant$ 35 kg/m^2 at the screening visit.

4. 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 assisted ventilation during the study).

5. Thymectomy therapy less than 3 months at the screening visit or may require thymectomy therapy during the study as judged by the investigator.

6. Thymic radiation therapy less than 3 months at the screening visit or possible need for thymic radiation therapy during the study at the discretion of the investigator.

7. Subjects treated with intravenous gamma globulin, plasmapheresis or plasmapheresis, with the last completed treatment less than 4 weeks prior to the Screening Visit.

8. Less than 6 months since last immunosuppressive monoclonal antibody drug therapy at the screening visit, including but not limited to rituximab, bevacizumab, Ecucizumab Etc. If B cell count was performed more than 6 months after the end of rituximab or bevacizumab, the B cell count did not return to above the lower limit of normal.

9. Splenectomized patients.

10. 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.

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

12. Has received a vaccine injection (including the COVID-19 vaccine) 4 weeks prior to the Screening Visit or is scheduled to receive a vaccine injection during the study.

13. 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.

14. 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.

15. At the screening visit: subjects with positive HBV surface antigen who did not receive treatment; subjects with positive HBV surface antigen who had received standard antiviral therapy (recommended to use Entecavir) for at least 2 weeks before the first dose of study drug (confirmed by medical documents) and promised to continue antiviral therapy during the study and 6 months after drug withdrawal; subjects without liver fibrosis or cirrhosis shown by abdominal B ultrasound (confirmed by medical documents if B ultrasound results within 30 days after drug withdrawal) can be excluded; subjects with negative HBV surface antigen and positive anti-HBV core antibody should be confirmed by quantitative detection of HBV-DNA ≤ 2000 IU/mL (confirmed by medical documents at screening visit or 12 weeks before screening visit).

16. Previous or current infection with Mycobacterium tuberculosis (positive interferon gamma release test 12 weeks before screening visit).

17. 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 ranges 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.

18. 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. Serum total IgG ≤ 6 g/L at screening visit;

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 (or corrected calcium) values exceeding 5% of the normal range.

e. Serum LDL-C ⩾ 4.9 mg/dL; subjects may be treated with lipid-lowering drugs prior to starting study medication, (Recommended use of ezelphos for lipid-lowering drugs),who can be enrolled.

19. 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.

20. Malignancy at any time, including bone marrow or lymphodysplastic disease, etc.

21. Patients who have undergone thymectomy within 12 months of the screening period; patients who have undergone thymectomy before 12 months and require chest CT examination to confirm no recurrence can be included. The results of CT examination with 30 days were accepted and medical documents were required.

22. Had an acute cardiovascular or cerebrovascular event (e.g., acute myocardial infarction, acute stroke, etc.) within 6 months prior to the screening visit.

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

24. Current or past 1 year alcohol or drug dependence/abuse, except nicotine and coffee.

25. 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.

26. 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.

27. 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)].

28. 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).

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

Administration criteria for the second treatment period (all of the following criteria must be met):

1. Subjects complete the first treatment period;

2. At Visit 11 of the first treatment period or at the last visit of the individualized follow-up period, subjects must:

≥ 4 weeks since last dose of trial drug; albumin ≥ 3.0 g/dL; and any of the following:

subject has < 3 point reduction in MG-ADL score from baseline; or b.MG-ADL score ≥ 5

3. No laboratory abnormalities that meet the criteria for suspension/discontinuation of study treatment.

Phase 2 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.

Phase 3 Study Drug:

Investigational Product: HBM9161 Injection

- Dose: 680 mg
- Method and route of administration:

First treatment period: Subcutaneous injection, QW for 6 doses;

Second treatment period: Subcutaneous injection, QW for 6 doses.

Phase 2 comparator:

Placebo

-Dose: N/A

-Method and route of administration: Subcutaneous injection, QW for the first 6 weeks, 6 doses in total

Phase 3 comparator:

Placebo

-Dose: N/A

-Method and route of administration:

First treatment period: Subcutaneous injection, QW for 6 doses;

Second treatment period: Subcutaneous injection, QW for 6 doses**.**

Phase 2 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)

Phase 3 Study Duration:

Total duration is expected to be approximately 26-30 weeks according to the patients' treatment cycles and efficacy persistence time.

Phase 2 STATISTICAL METHODS:

The primary objectives of this phase include the clinical verifying of the mechanism of action of the drug, providing the basis for entering the phase 3, and supporting the dose selection and safety evaluation of the phase 3. 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 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. The dose selection of phase 3 will be based on efficacy, safety and pharmacology consideration.

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.

In addition, due to the need for the initiation of phase 3, the second interim analysis will be performed when all subjects have completed the 6-week assessment. The scope of the second interim analysis is similar to that of the first interim analysis. The only difference is that all subjects will be included. The remaining part of phase 2 will not be changed with the results of this interim analysis.

Phase 3 Statistical Methods:

This stage is a group sequential statistical design, and the statistical hypothesis test will be performed at 1-sided of overall 0.025 significant level for efficacy endpoints. Trial sample size is based on the primary efficacy endpoint (i.e. sustained MG-ADL response rate within 9 weeks) in the population of AChR-Ab positive or MuSK-Ab positive patients, and the target power of the trial is 90%. An interim analysis will be performed when the first 67% (approximately 80 cases) of autoantibody-positive patients complete primary endpoint assessment. The overall class I error of statistical hypothesis testing is controlled by the Hwang-Shih-DeCani α-spending function; if statistical significance is reached at the significance level at 1-sided of 0.0063 in interim primary analysis, it can be considered that the trial is terminated prematurely (the follow-up of enrolled subjects is continued), otherwise the trial is continued, and 1-sided of 0.0230 level of significance will be applied in the final analysis. If the test for the primary endpoint is statistically significant, the sequential testing of full population will be treated at the same significance level (i.e., including both antibody-positive and antibody-negative populations). If the statistical test of full population is also statistically significant, the sequential testing will be performed at the significance level of 1-sided of 0.0159 (i.e., P Ocock Border) for remaining secondary efficacy endpoints.

The statistical hypothesis of dichotomous data will be statistically tested with normal distribution approximation, and the same normal distribution approximation will also be used for the calculation of 95% confidence interval. Missing assessments in the primary analysis will be imputed as not meeting the response threshold, and efficacy responses achieved after rescue treatment use will be treated as not meeting the efficacy response condition in the statistical analysis.

Descriptive statistics will be used for continuous data, and further analysis will be performed according to appropriate statistical analysis method (such as Kaplan-Meier, etc.).

An external independent data monitoring committee (iDMC) will be responsible for the conduct of the interim analysis and data review, and the independent data monitoring committee charter and interim statistical analysis plan (including iDMC recommended guidelines) will be finalized prior to enrollment of the first subject in Phase 3.

Phase 2 Population pharmacokinetics and dose-response analysis:

All HBM9161 plasma concentration data obtained in this phase will be used in the PopPK analysis (using nonlinear mixed effects modeling [NONMEM]) in combination of already obtained PK data 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.

Phase 3 Population pharmacokinetics and dose-response analysis:

The available PK and PD data for HBM9161 will be combined to develop a PopPK/PD model to further characterize the quantitative relationship between PK and/or PD and efficacy and/or safety measures. The impact of demographic characteristics, disease progression, and concomitant medications on PK and/or PD characteristics will be investigated systematically and quantitatively.