CLINICAL TRIAL PROTOCOL SYNOPSIS

HBM4003

Version No ./date: 1.0/May 14, 2021

Study No.: 4003.6

Protocol title:

An Open-Label, Phase 1 Clinical Study to Evaluate the Safety, Tolerability, PK/PD and Preliminary Efficacy of HBM4003 in Combination With Toripalimab in Patients With Advanced NEN and Other Solid Tumors

Period: Phase 1

Country and Site: China, multicenter

Rationale:

CTLA-4 (CD 152) is an inhibitory immune checkpoint receptor that attenuates T-cell receptor signaling by impeding the CD28-B7 costimulatory pathway, which is essential for full T-cell activation during the priming phase (Linsley et al., 1994; Krummel and Allison, 1995; van der Merwe et al., 1997). Treg cells also significantly express CTLA-4, the strongest suppressor of anti-tumor immunity, which mediates the down-regulation of CD80 and CD86 expression in antigen-presenting cells (Ni L and Dong C, 2017). Therefore, CTLA-4 plays a key role in immune tolerance and negative regulation of immune response (Gibson et al., 2007).

Immune checkpoint blocking drugs for CTLA-4, PD-1, and PD-L1 have become an important part of cancer therapy (Pardoll, 2012). Ipilimumab is the only CTLA-4 blocking antibody currently approved by the US Food and Drug Administration (FDA) for marketing for the treatment of advanced melanoma. CTLA-4 inhibits the early activation of T cells (mainly in lymph nodes), while PD-1 regulates the killing activity of T cells (mainly in tumors), and combination therapy against both has a synergistic effect (Galon and Bruni, 2019). Nivolumab (nivolumab), a PD-1 monoclonal antibody, has been used in the treatment of patients with hepatocellular carcinoma, melanoma, renal cell carcinoma, hepatocellular carcinoma, and metastatic colorectal cancer with microsatellite instability-high/mismatch repair deficiency (Yervoy 2020 and Opdivo 2019). The clinical efficacy of ipilimumab increases with increasing dose; however, the toxicity of ipilimumab is also dose-dependent, and its use can be limited by potentially life-threatening adverse effects (Haanen et al 2017). As a PD-1 monoclonal antibody developed by China itself, teripilumab has demonstrated its controllable safety and preliminary clinical response rate in Chinese patients with inoperable locally advanced or metastatic melanoma, recurrent/metastatic nasopharyngeal carcinoma who have failed two or more previous systemic therapies, and locally advanced or metastatic urothelial carcinoma who have progressed within 12 months after failure of platinum-based chemotherapy including

neoadjuvant or adjuvant chemotherapy, and has obtained the conditional approval for marketing by China Food and Drug Administration.

Over the past few years, multiple studies have reassessed CTLA-4 checkpoint blockade strategies in cancer immunotherapy. Complete CTLA-4 occupancy, systemic T cell activation, and significant autoreactive T cell proliferation are not necessary for tumor rejection, but are associated with immune-related adverse effects (Du et al 2018). In different human tumors, the clinically effective anti-CTLA-4 monoclonal antibody increased the density of CD4 and CD8 positive T cells in the tumor, but did not significantly clear FOXP3 positive Treg (Sharma A et al., 2019).

The results represent a new method for the development of second-generation anti-CTLA-4 monoclonal antibodies in cancer immunotherapy by selectively enhancing local Tregs clearance. The new generation of anti-CTLA-4 monoclonal antibody is designed to improve clinical safety by reducing systemic exposure and to provide better clinical efficacy by enhancing the clearance of intratumoral Treg cells through antibody-dependent cell-mediated cytotoxicity (ADCC) effect.

The recombinant fully human monoclonal heavy chain antibody HBM4003 immediately used the above design idea to enhance Treg clearance effect by blocking the CTLA-4 pathway and enhancing ADCC. In the MC38 tumor-bearing model in hCTLA-4 KI mice, HBM4003 showed better efficacy than the ipilimumab analogue in preclinical in vivo trials, mainly by virtue of its potent TIL-Treg clearance effect (not by ipilimumab) and bioactivity comparable to that of ipilimumab (in vitro CTLA-4 binding and blockade). In the GLP toxicity study, HBM4003 was well tolerated, with the highest nonseverely toxic dose (HNSTD) of 3 mg/kg. Given the improved efficacy of HBM4003 in vivo, HBM4003 has a better benefit/risk profile than ipilimumab.

The proposed 4003.6 study is a sub-study of the approved and ongoing 4003.2 study, which is mainly a clinical trial of the combination of HBM4003 and Tipilimumab in patients with advanced neuroendocrine tumors and other solid tumors to explore the clinical evidence of dual immunotherapy and to further focus on studying and improving the unmet clinical treatment needs of patients with advanced neuroendocrine tumors. If 4003.2 has completed the dose escalation part and determined the RP2D at the time of 4003.6 study initiation, 4003.6 can directly use this RP2D to enter the Part 2 - Dose Expansion Stage after discussion and confirmation by SRC.

Objectives:

Part 1: Dose Escalation Phase to Determine the Highest Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D) of HBM4003 in Combination with Tiprilimumab in Patients with Advanced Neuroendocrine Tumors and Other Solid Tumors	
Study objectives	Study Endpoints
Primary objective	Primary endpoint

1. To evaluate the safety and tolerability of HBM4003 in combination with teriprilumab in patients with advanced neuroendocrine tumors and other solid tumors;	• MTD and/or RP2D of HBM4003 in combination with Toripalimab; • Number of Subjects with DLTs During the First Treatment Cycle (21 Days) at Each Dose .

Secondary objectives	Secondary endpoints
1. To evaluate the preliminary efficacy of HBM4003 in combination with teriprilumab in patients with advanced neuroendocrine tumors and other solid tumors; 2. To evaluate the pharmacokinetics (PK) of HBM4003 in patients with advanced neuroendocrine tumors and other solid tumors; 3. To evaluate the immunogenicity of HBM4003 in combination with Toripalimab in patients with advanced neuroendocrine tumors and other solid tumors; 4. To exploratively characterize the population PK profile of HBM4003 in combination with Toripalimab in patients with advanced neuroendocrine tumors and other solid tumors based on a population PK analysis approach; 5. To assess the relationship between exposure to HBM4003 and efficacy and adverse events, if available. The relationship between exposure to Toripalimab and efficacy and adverse events (AEs) will also be assessed. 6. To explore the pharmacodynamic (PD) parameters and biomarkers of HBM4003 in combination with Toripalimab in patients	• Objective response rate (ORR): including the proportion of patients with complete response (CR) and partial response (PR); • Disease control rate (DCR): including the proportion of patients with complete response (CR), partial response (PR) and stable disease (SD); • Duration of response (DOR) [calculated from the first occurrence of confirmed CR or PR until the date of disease progression or (due to any cause) death]; • Duration of Disease Control (DDC) [for subjects with CR, PR, or SD, duration is calculated from the time of initial dose until the date of disease progression or death due to any cause]; • PK parameters of HBM4003 (Cmax, Tmax, AUC0-last, AUC0-tau, if applicable, AUC0-inf, t1/2, Vd, CL, etc.); • Immunogenicity, including the incidence of positive anti-drug antibodies (ADAs), of HBM4003 and teriprilumab. For those with positive anti-drug antibodies, the incidence of neutralizing antibodies (Nab) was detected. • All the plasma concentration data of HBM4003 obtained in this study will be used for population PK analysis, and a PK model will be established to characterize the PK characteristics of HBM4003; • Dose-response assessment: to explore correlation between PK/efficacy and PK/safety, if applicable • Descriptive statistics for biomarker assessment, such as cell biomarkers, cytokines, PD-L1 expression, tumor microenvironment markers, etc.

with advanced neuroendocrine tumors and other solid tumors.	• Other possible endpoints [such as tumor mutation burden (TMB)] will not be presented in the final report of this trial.

Part 2: Dose expansion phase to assess the preliminary efficacy and safety of the combination of HBM4003 and teriprilumab in patients with advanced neuroendocrine tumors at the RP2D dose.	
Study objectives	Study Endpoints
Primary objective 1. To evaluate the preliminary efficacy of HBM4003 in combination with teriprilumab in patients with advanced neuroendocrine tumors;	Primary endpoint • ORR per RECIST 1.1: includes the proportion of patients with CR and PR.
Secondary objectives 1. To evaluate the safety of HBM4003 in combination with Toripalimab in patients with advanced neuroendocrine tumors; 2. To evaluate the long-term efficacy of HBM4003 in combination with teriprilumab in patients with advanced neuroendocrine tumors; 3. To evaluate the immunogenicity of HBM4003 in combination with teriprilumab in patients with advanced neuroendocrine tumors; 4. To characterize the population PK of HBM4003 in combination with Toripalimab in patients with advanced neuroendocrine tumors who have failed standard therapy based on a population PK analysis approach;	Secondary endpoints • Number of patients with at least one treatment-related AE; • Proportion of patients with DCR per RECIST 1.1; • DOR per RECIST 1.1 [calculated as the duration from the first occurrence of confirmed CR or PR until the date of disease progression or (due to any cause) death]; • DDC per RECIST 1.1 [for subjects with CR, PR, or SD, duration is calculated from time of initial dose until date of disease progression or death due to any cause]; • Overall survival (OS): the length of time from the start of treatment to the time a subject dies (from any cause); • Progression-free survival (PFS) per RECIST 1.1: length of time from start of treatment until disease progression or death from any cause; • Immunogenicity of HBM4003 and Toripalimab, including the incidence of positive ADAs. For those with positive anti-drug antibodies, the incidence of Nab was tested. • All the plasma concentration data of HBM4003 obtained in this study will be used for population PK analysis, and a PK model will be established

5. To assess the relationship between exposure to HBM4003 and efficacy and AEs, if available. The relationship between exposure to Toripalimab and efficacy and AEs will also be assessed. 6. To evaluate PD parameters and biomarkers of HBM4003 in combination with Toripalimab in patients with advanced neuroendocrine tumors.	to characterize the PK characteristics of HBM4003; • Dose-response assessment: to investigate the relationship between PK/efficacy and PK/safety, if applicable; • Descriptive statistics for biomarker assessment, such as cell biomarkers, cytokines, PD-L1 expression, tumor microenvironment markers, etc. • Other possible endpoints (such as TMB) will not be presented in the final report of this trial.

Study Design:

Part 1 - Dose Escalation Phase to determine the MTD and/or RP2D of HBM4003 in combination with teriprilumab in patients with advanced neuroendocrine tumors and other solid tumors.

Screening Period

After signing the informed consent form, patients will be screened for eligibility within 28 days before starting study medication. Subject eligibility will be assessed after all screening procedures have been completed.

Treatment period

A 21-day treatment cycle. HBM4003 will be administered once on Day 1 of each treatment cycle. One dose of fixed dose mg each time is administered on Day 1 of each treatment cycle of teriprilumab.

The DLT observation period was defined as 21 days of the first treatment cycle. After the end of DLT observation period, if no DLT event occurs, the subjects will continue to receive treatment with HBM4003 in combination with Toripalimab for a maximum treatment period of 2 years, or withdraw from the trial until confirmed disease progression, intolerance, or withdrawal of informed consent, whichever occurs first. Subjects may permanently discontinue HBM4003 during the study due to an adverse event, while only treatment with Toripalimab is administered in subsequent treatment cycles (see 14.4 Appendix: Management of Immunotherapy-related Toxicities for details).

In the 4003.1 study, the starting dose of HBM4003 was 0.3 mg/kg QW. As of April 13, 2021, a total of 20 subjects were treated in the dose escalation phase of 4003.1 study, of which 7 subjects were treated with 0.3 mg/kg weekly HBM4003, 7 subjects were treated with 0.45 mg/kg every 3 weeks HBM4003, and 6 subjects were treated with 0.6 mg/kg every 3 weeks

HBM4003. The maximum tolerated dose (MTD) has not been reached. Except for 1 patient in the 0.3 mg/kg dose group and 2 patients (1 in the 0.45 mg/kg and 1 in the 0.6 mg/kg dose groups) who could not be evaluated, no other patients had DLT. In the 4003.2 study, a dose escalation study was conducted using HBM4003 0.03 mg/kg Q3W as the starting dose in combination with terpilimumab fixed dose mg Q3W. In the accelerated titration phase of the trial HBM4003 0.03 mg/kg, only one subject will be enrolled, and if no DLT occurs in this subject, the dose can be escalated to the 0.1 mg/kg dose group; from the 0.1 mg/kg dose group, dose escalation will be guided by the i3 + 3 principle. As of April 21, 2021, one patient in HBM4003 0.03 mg/kg group had no DLT, and two patients in HBM4003 0.1 mg/kg group had completed the administration once, without DLT. In this study, considering the potential safety risks of the combination in combination with the dose escalation results of 4003.1 and 4003.2, 0.03 mg/kg was selected as the initial dose of the combination in this study to ensure the safety of subjects. This starting dose will be reasonably changed after discussion by SRC if necessary, based on the clinical safety, tolerability and PK data of this product in 4003.1 and 2021.2 studies.

Dose Escalation Schedule

Group	1 (n = 1)	2 (i3 + 3)	3 (i3 + 3)	4 (i3 + 3)	5 (i3 + 3)	6 (i3 + 3)
HBM4003 (mg/kg)	0.03	0.1	0.3	0.6	1.0	1.5
TERPRELIMAB (mg)	fixed dose	fixed dose	fixed dose	fixed dose	fixed dose	fixed dose

During the dose escalation process, adjustments may be made to the preset escalating dose levels, dosing frequency, total number of HBM4003 doses, and PK blood sampling points based on safety, efficacy, and human PK data, as discussed by the SRC.

Dose escalation and de-escalation principles

One subject was enrolled in the first cohort. If the subject had DLT, two more subjects were enrolled in this cohort. The principle of dose escalation and de-escalation was changed to i3 + 3 as below. Beginning with Group 2, 3 subjects were enrolled in each cohort. From Group 2 onwards, after each cohort completes the DLT observation period, the i3 + 3 algorithm is used to guide dose escalation or de-escalation based on the number of all subjects with DLT at the current dose level. In this experiment, the target DLT probability of MTD is set as 25%, the equivalence interval of DLT probability is 20% ~ 30%, and the maximum sample size is 31. Details of the statistical algorithm are provided in the statistical methods section. The following table shows possible scenarios for up to 12 subjects at a dose level.

	1	2	3	4	5	6	7	8	9	10	11	12
0	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**

1	S	S	S	S	S	E	E	E	E	E	E	E
2		DU	D	D	D	S	S	S	S	S	E	E
3			DU	DU	DU	D	D	D	D	S	S	S
4				DU	DU	DU	DU	DU	D	D	D	D
5					DU	DU	DU	DU	DU	DU	D	D
6						DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

* Column shows the number of patients treated. Rows represent the number of patients with DLT.

* E: Upgrade to the next higher dose; S: Keep the same dose; D: Downgrade to the previous lower dose, keep the same dose if the current dose is the lowest dose; DU: Downgrade to the previous lower dose, the current dose will not be used in this trial.

The specific steps are as follows:

1. start the trial and enroll one subject at the starting dose. If no DLT occurred in this subject, 3 subjects were enrolled in each cohort starting from Group 2. After DLT evaluation results are observed for each subject, dose escalation, reduction or maintenance will be performed according to the above table.
2. dose escalation will end when any of the following conditions are met:
   a. 31 subjects have completed the study;
   b. 9 subjects have been studied at the next dose level to be decided;
   c. At the lowest dose level, Assessment by DLT Is "DU".

Definition of DLT

The DLT observation period was defined as 21 days of the first treatment cycle. A DLT was defined as any of the following AEs at least possibly related to study drug (IP) that met the protocol-defined CTCAE 5.0 severity criteria and occurred during the DLT observation period.

- One or more of the following hematological toxicities (only toxicities clearly related to the underlying disease or concurrent illness can exclude DLTs):
  - Grade 4 anemia;

- Grade 4 leukopenia;
- Grade 4 leukocytosis or grade 3 leukocytosis lasting ⩾ 7 days;
- Grade 4 neutropenia;
- ⩾ Grade 3 febrile neutropenia;
- Grade 4 thrombocytopenia.

— Any grade 3 or higher non-hematological toxicity (DLT can be excluded only for toxicities significantly related to the underlying disease or concomitant diseases), except:

- Alopecia of any grade;
- Grade 3 fatigue, and recovered to ⩽ Grade 2 at Grade 2;
- Grade 3 insomnia, diarrhea, and vomiting that resolved to ⩽ Grade 2 in 72 hours.

— Any serious life-threatening complication or abnormality observed during the first treatment cycle that was not defined in CTCAE version 5.0 and could be attributed to the study medication.

— Any other AE not mentioned above that, in the opinion of the investigator, poses a safety hazard to the subject may also be assessed and considered a DLT, e.g.:

- Permanent discontinuation of HBM4003 due to treatment-related toxicity;
- AEs requiring treatment with systemic corticosteroids equivalent to prednisone ⩾ 10 mg/kg, including but not limited to Grade 1 and higher neurologic toxicities (eg, aseptic meningitis, encephalitis, and transverse myelitis), hematologic toxicities (eg, acquired thrombotic thrombocytopenic purpura, aplastic anemia, and acquired hemophilia), and cardiac toxicities (eg, myocarditis, pericarditis, arrhythmias, ventricular compromise with heart failure, and vasculitis).

Determination of MTD and RP2D

1. MTD: After the end of the trial, isotonic (isotonic) regression was applied to select the MTD (i.e. Guo et al., 2017). I.e. selected toxicity Profile The isotonic estimate of the rate is closest to Target Probability of Toxicity Of the dose as the MTD. If the isotonic estimates of the two toxicity probabilities are equally close to the target toxicity probability, the isotonic estimate of the low toxicity probability is selected. If the isotonic estimate of the probability of two doses of toxicity is consistent, the higher dose is selected as the MTD if the estimate is less than the target toxicity probability, and the lower dose is selected as the MTD if the estimate is greater than or equal to the target toxicity probability.

2. RP2D: Conventional guidelines for assessing MTD may not be applicable for immunotherapeutic agents. After consultation with the SRC, the sponsor may choose to determine the RP2D in combination with other relevant data. The RP2D may be less than or equal to the MTD.

Part 2 - Dose expansion phase to assess the preliminary efficacy and safety of HBM4003 in combination with teriprilumab at the RP2D in patients with advanced neuroendocrine tumors.

In part 1, after the dose escalation study of HBM4003 in combination with TERPRELIZUMAB was reviewed and recommended by SRC and approved by the Ethics Committee, and the MTD (or RP2D) was jointly confirmed by the principal investigator (PI) and the sponsor, part 2 was conducted to evaluate the preliminary efficacy and safety of HBM4003 in combination with TERPRELIZUMAB at the RP2D of HBM4003 in patients with advanced neuroendocrine tumors. If at the time of 4003.6 study initiation, the RP2D has been determined in 4003.2 study, it can be used directly after discussion and confirmation by SRC. Subjects in the dose expansion phase will be treated with HBM4003 at the RP2D dose in combination with Toripalimab until 1 year after the last study drug intake, or initiation of new antineoplastic therapy, or confirmation of disease progression, whichever occurs first. Subjects may permanently discontinue HBM4003 during the study due to an adverse event, while treatment with only Toripalimab is administered in subsequent treatment cycles (see Appendix 14.5: Management of Immunotherapy Related Toxicities for details).

Inclusion/exclusion criteria

Primary Inclusion criteria:

1. Males or females aged ≥ 18 years at the time of signing the informed consent form. For Part 1 of this study, the subjects should be ≤ 75 years of age.
2. Patients for Part 1: patients histopathologically diagnosed with advanced or recurrent solid tumors.
3. For Part 2 of the study, Patients with non- functional metastatic neuroendocrine tumor confirmed by histopathology.
4. Patients must be able to provide archived tumor tissues after latest treatment or fresh tumor tissues and relevant pathology report.
5. Patients whose estimated survival time is more than 3 months.
6. Patients with at least one measurable lesion at baseline according to RECIST (Version 1.1). The lesion had not previously received surgery, radiotherapy and/or local treatment.
7. Patients with Eastern Cooperative Oncology Group(ECOG) performance status score ≤1.
8. Every woman or man with potential fertility needs to use an effective contraceptive method during the study, up to within 3 months after last drug administration.
9. Willing and able to comply with study-specified visits schedule, treatment plan, laboratory examination and other study procedures.

Primary Exclusion criteria:

1. Patients who are simultaneously participating in another clinical study.
2. Patients with a history of severe allergic diseases, a history of severe drug allergies, and known or suspected allergy to macromolecular protein preparations or HBM4003 or toripalimab or its excipients.
3. Previous and concomitant drugs or treatments to be excluded like:

    - Anti-CTLA4 drug;
    - For part 1, anti-PD1 anti-PDL1 or anti-PDL2 treatment was received within 8 weeks prior to the start of the study;
    - For part 2, patients received anti-PD1, anti-PDL1 or anti-PDL2 treatment during the relapse or metastasis stage, and the time from the last treatment is short than 12 months before the first dose;
    - Received other antitumor treatment (including chemotherapy, radiation, targeted therapy, or biotherapy), antitumor vaccine, chinese herbal medicine or proprietary medicine with anti-tumor effect, Immunosuppressant or glucocorticoid, Transfusion of PLT or RBC prior to initiation of study treatment;
    - live attenuated vaccine was received before study administration or planned during the study period.

4. Insufficient recovery from previous treatments.
5. Diseases that may affect the efficacy and safety of the investigational product, including but not limited to active infection, active autoimmune disease or autoimmune disease, primary immunodeficiency disease, any clinically significant cardiovascular disease, severe pulmonary insufficiency, organ transplantation, etc.
6. A history of other malignant diseases within 5 years before the first dose.
7. Symptomatic, active, or urgent treatment-requiring central nervous system (CNS) metastasis with imaging evidence (based on CT or MRI assessment).
8. Subjects with pleural effusion, pericardial effusion, or ascites that could not be stabilized by repeated drainage or other methods were determined by investigator.
9. Patients who the investigator believes may have other factors that will affect the efficacy or safety evaluation of this study (e.g., mental disorders, alcoholism, drug use, etc.).
10. Women who are pregnant or breastfeeding, or who plan to become pregnant during the study period and within 3 months after the last administration of the investigational product.

Investigational Product (IP):

HBM4003 is supplied as a liquid intravenous dosage form in 20 mg/mL, 4 mL/vial.

- Dose: Dose levels for the dose escalation phase are presented in the dose escalation schedule. In the dose expansion phase, the RP2D determined in the escalation phase serves as the expansion dose.
- Usage: Intravenous infusion, every 21 days as a treatment cycle. See the dose escalation schedule for details.

Terapril Injection, strength 40 mg/ml, 6 ml/vial.

- Dose: fixed dose once every 21 days in both dose escalation and dose expansion phases.
- Usage: Intravenous infusion, every 21 days as a treatment cycle. For the method of product dilution and intravenous drip administration, please refer to the package insert.

Control Product:

Not applicable for this study.

Duration of treatment:

Individual Subject Treatment Duration

Study drug will be administered on Day 1 of each 21-day treatment cycle. For subjects in whom disease progression was observed, treatment could continue if the patient had stable or decreasing clinical symptoms and clinical benefit was determined by the investigator and confirmed by the sponsor. Each subject will receive study drug for a maximum of 2 years or until confirmed disease progression, confirmed inability to benefit from therapy, intolerance, or withdrawal of consent, whichever occurs first.

The expected duration of treatment for each subject will vary based on the number of cycles completed; the number of cycles will depend on whether the subject is benefiting from the treatment. The study consists of a 4-week screening period, a 21-day treatment cycle (which can be repeated depending on the potential for clinical benefit), an EOT visit after treatment discontinuation, and 2 subsequent visits 28 days (± 7 days) and 84 days (± 7 days) after the last dose of study medication.

Study End Time

The end of the entire study is defined as 12 months after the last dose of study drug for the last subject.

Assessment:

Safety Assessments

Safety assessments included monitoring and recording of all AEs and serious adverse events (SAEs), physical examinations, ECOG performance status, vital signs including pulse rate and blood pressure, 12 electrocardiograms, echocardiograms (to examine LVEF), hematology tests, clinical chemistry tests, urine tests, and concomitant medications.

In Part 1, the number of patients with DLTs during Cycle 1 (21 days) after the first dose

of study drug at each dose level.

Tumor response assessment

Tumor response is assessed according to RECIST 1.1 (and mRECIST for patients with hepatocellular carcinoma) during study treatment. Tumor assessments will be performed at baseline, every 6 weeks (± 1 week) for 12 months prior to first study drug administration, and every 12 weeks (± 2 weeks) thereafter for a maximum of 12 months from study drug administration, or until new therapy is initiated, radiographic disease progression per RECIST 1.1 is documented (Eisenhauer et al, 2009), or the subject continues treatment with study drug after disease progression per RECIST 1.1 but is no longer of clinical benefit in the judgment of the investigator, whichever occurs first.

Magnetic resonance imaging (MRI) may be used in exceptional cases. For each subject, it should be ensured that the same imaging method is used for efficacy evaluation throughout this study.

Evaluation of Pharmacokinetics (PK)

The plasma concentrations of HBM4003 and Tiprilizumab will be collected and analyzed at specific blood sampling time points as shown in the study flow chart.

The kinetic parameters of HBM4003, including Cmax, Tmax, AUC0-tau, AUC0-inf, t1/2, Vd, CL, etc. will be evaluated in subjects in dose escalation group and during multiple dose administration.

In addition, all HBM4003 plasma concentration data obtained in this study will be used for population PK analysis to develop a PK model to characterize the PK profile of HBM4003. Population pharmacokinetic (popPK) results will be reported separately.

Dose-Response Assessment

Individual subject exposure parameters were estimated based on the parameter estimates from the final PK model developed for further dose-response (exposure-response) analyses, including PK/efficacy and PK/safety correlation analyses. The relationship between exposure to Toripalimab and efficacy and adverse events will also be assessed. Results of these analyses will be reported separately.

Immunogenicity Assessment

ADAs for HBM4003 and teripilimumab will be collected and analyzed at specific blood collection time points as described in the Study Flow Chart. For ADA positive individuals, neutralizing antibodies will be analyzed.

Pharmacodynamic (PD) and Biomarker Assessments

Pharmacodynamic and blood biomarker assessments will be collected and analyzed at specific blood collection time points as specified in the Study Flow Chart.

The subject must provide fresh tumor tissue specimens before the first dose of study drug or archived tumor tissue specimens (formalin-fixed paraffin-embedded [FFPE] tissue blocks or at least 8 unstained FFPE slides) after the most recent treatment for the detection of exploratory indicators such as PD-L1 expression and tumor microenvironment markers. If a subject is

unable to provide a fresh tumor sample or archived tumor tissue sample after the most recent treatment, and only an archival tumor sample before the most recent treatment, the PI will discuss with the sponsor to determine whether the subject can be enrolled in the study. If there are lesions that can be biopsied and the risk of the biopsy procedure is acceptable, it is encouraged to provide a fresh tissue specimen for comparative analysis at the Week 6 CT/MRI tumor response assessment. If tumor biopsy is not performed at Week 6, tumor biopsy is encouraged at 28 days (± 7 days) after last dose of study drug.

See Section 8.13 and Laboratory Manual for details of the biomarker test items to be analyzed.

Safety Review Committee (SRC):

In Part 1, the SRC will review all subjects for clinical relevance of safety data at the end of the first treatment cycle at each dose level and its relationship to HBM4003 treatment.

Based on the safety information, the SRC will make recommendations regarding the continuation, modification, or termination of the study. The right to discontinue, modify, or terminate the study remains with the sponsor. Details on the SRC will be described in a separate document.

Statistical Analysis Methods:

The design consists of two parts, with Part 1 being dose escalation to determine the dose to be administered in the Part 2 dose expansion design.

The dose escalation phase will use the i3 + 3 algorithm to guide dose decisions. The MTD will be determined by isotonic regression estimation.

Descriptive and exploratory statistical analyses will be used in both the dose escalation and dose expansion phases.