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STATISTICAL ANALYSIS PLAN

Protocol Title

Single Center, Open label, Repeat Intramuscular Administration, 270days, Phase I/2a Clinical Trial to Evaluate Safety and Tolerability of Investigational Product (Engensis: VM202) in Patients with Charcot-Marie-Tooth Disease Subtype 1A (CMT1A)

Protocol No.

VMCMT-001

Investigational Product

Engensis: VM202

Effective Date

Date of Signing of Final Approving Authority

Version No/Date

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Written By

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Statistical Analysis Plan

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Abbreviation

Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Events
ALT	Alanine Transaminase (SGTP)
AST	Aspartate Transaminase (SGOP)
ATC code	Anatomical Therapeutic Chemical code
BMI	Body Mass Index
CMAP	Compound Muscle Action Potential
CMT	Charcot-Marie-Tooth disease
CMT1A	Charcot-Marie-Tooth disease subtype 1A
CMTNS-v2	Charcot-Marie-Tooth Neuropathy Score Version 2
FAS	Full Analysis Set
HCT	Hematocrit
HGF	Hepatocyte Growth Factor
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intent-to-Treat
KGCP	Korea Good Clinical Practice
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	Mean Platelet Volume
MRI	Magnetic Resonance Imaging
NCV	Nerve Conduction Velocity
NCAM	Neural cell adhesion molecule 1
ONLS	Overall Neuropathy Limitation Scale
PPS	Per-Protocol Set
PT	Preferred Term
PV	Pharmacovigilance
p75	p75 Neurotrophin receptor
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNAP	Sensory Nerve Action Potential

Term	Definition
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
10MWT	10-meter walk test
WBC	White Blood Cell
WHOART	WHO Adverse Reactions Terminology

Contents

1. Objective and Background of Clinical Study

Single Center, Open label, Repeat Intramuscular Administration, 270days, Phase I/2a Clinical Trial to Evaluate Safety and Tolerability of Investigational Product (Engensis: VM202) in Patients with Charcot-Marie-Tooth Disease Subtype 1A (CMT1A)

1.1 Objective of Clinical Study

To assess the safety and tolerability of the investigational product (VM202) injected in the weakened lower limb muscles of CMT1A patients.

1.1.1 Primary Objective

To evaluate safety and tolerability following repeated doses of the investigational product (VM202).

1.1.2 Secondary Objectives

To evaluate efficacy following repeated doses of the investigational product (VM202).

(1) Changes in severity of disease
- CMTNS-v2 (Charcot-Marie-Tooth Neuropathy Score version 2)
- FDS (functional disability scale)

(2) Changes in lower limb function
- ONLS (overall neuropathy limitation score) leg scale
- 10MWT (10-meter walk test)

(3) Changes in fatty infiltration level of lower limb muscles
- MRI leg

(4) Nerve regeneration potential
- CMAP (compound motor nerve action potential)
- SNAP (compound sensory nerve action potential)
- NCV (nerve conduction velocity)

(5) HGF antibody generation by VM202

1.2 Clinical Study Design

The progression and procedures of this clinical study are as shown in the figure below.


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Figure 1. Schematic diagram of clinical study

1.3 Clinical Study Subjects

1.3.1 Inclusion Criteria

Subjects enrolled in this clinical study must satisfy all of the following inclusion criteria:

1) Males and females ≥ 19 years of age and ≤ 65 years of age
2) Patients with confirmed diagnosis of CMT1A by genetic testing
3) Patients with mild-to-moderate severity assessed by Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS-v2) with a score > 2 and ≤ 20
4) Individuals with lower limb muscle weakness with minimum dorsiflexion or more
5) Individuals who voluntarily consented to participate in this study and signed the IRB-approved informed consent form after listening to a description on the characteristics of this clinical study prior to all screening tests
6) Individuals who can comply with the requirements in the clinical study
7) In case of females of child-bearing potential, those who test negative in a urine or serum pregnancy test at screening
8) Individuals who practice medically approved contraceptive methods* throughout the clinical study

*Definitions

- Drug: Oral contraceptives, skin patches, or progestin formulations (implants or injections)
- Barrier method: Condoms, diaphragms, intrauterine devices (IUDs), vaginal suppositories
- Sexual abstinence: Complete abstinence (However, periodic abstinence (e.g., calendar method, ovulation method, and sympto-thermal method) and self-restraint are not considered as acceptable methods of contraception.)

1.3.2 Exclusion Criteria

Subjects will be excluded from this clinical study if any one of the following criteria is met:

1) Patients with significant respiratory, circulatory, renal, gastrointestinal, hepatic, endocrine, hematologic, psychiatric disorders or other severe diseases, or alcohol or drug addiction who may develop safety issues or cause confusion in the interpretation of the clinical study results as determined by the principal investigator
2) Patients with other neuromuscular diseases or neuropathy-inducing factors: Patients with chronic alcohol addiction, undergoing anticancer chemotherapy, or taking neurotoxic drugs
3) Patients diagnosed with diabetes
4) Patients diagnosed with inflammatory bowel disease
5) Patients with a history of stroke or cerebral ischemic attack within 12 months prior to the screening date

6) Patients with a history of coronary artery disease, such as myocardial infarction and unstable angina pectoris, within 12 months prior to the screening date
7) Morbidly obese patients with body mass index (BMI) ≥ 37
8) Patients who underwent orthopedic surgery (corrective surgery for bone and ligament, artificial joint implantation, osteosynthesis, osteotomy, arthroscopic surgery) in the lower limbs within 6 months prior to the screening date
9) Patients who may be affected by the muscle strength measurement test due to ankle contracture or surgery
10) Patients with uncontrolled hypertension (if systolic blood pressure is ≥ 160 mmHg or diastolic blood pressure is ≥ 100 mmHg at screening)
11) Within the last 5 years prior to the screening date, patients or patient's immediate family members (parents, siblings, offspring) with a history of malignant tumors, excluding basal cell carcinoma or squamous cell carcinoma that occurs on the skin (if it is determined that there is no possibility of relapse after resection), or with a family history of familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC)
12) Patients who have not completed a national cancer screening program applicable to their sex and age (date of birth) (if it cannot be confirmed that the relevant test was received at a national cancer screening center or a recognized screening center)

    However, if it is confirmed that the relevant test was received at a national cancer screening center or a recognized screening center during the screening period, and that the results were within normal range, the patients may participate in the clinical study.

    Common to males and females: If a patient is ≥ 50 years of age, the results of a colonoscopy within 5 years prior to the screening must be determined as being within normal range, and if adenomatous polyps are evident, the results of a colonoscopy within 1 year must be determined as being within normal range (inflammatory polyps or hyperplastic polyps are included in the normal range). If a patient is ≥ 40 years of age, the results of a gastroscopy within 2 years prior to the screening must be within normal range. If a patient is ≥ 54 years of age and has a 30 pack-year history of smoking or more, the results of a low-dose chest CT within 2 years prior to the screening must be within normal range. In case of liver cancer, carriers of hepatitis B or hepatitis C virus and patients with hepatic cirrhosis fall under the exclusion criteria. Females: For females ≥ 40 years of age, normal range findings must be confirmed in a mammogram within 2 years. For females ≥ 20 years of age, normal range findings must be confirmed in a Pap smear within 2 years.

13) Patients diagnosed with active pulmonary tuberculosis
14) Patients with HBV or HCV
15) Patients who test positive in human immunodeficiency virus (HIV) antibody test
16) Patients in an immunocompromised state due to treatments such as immunosuppressants, anticancer chemotherapy, and radiotherapy
17) Patients with a history of mental disease, which may interfere with study participation, within 6 months prior to the screening date
18) Patients who must take medications, that are known to have significant drug interactions within 14 days after the first administration of the investigational product or deemed unsuitable by the investigator's judgment
19) Individuals who participated in another clinical study* within 6 months from the time of screening

*Definitions

- Drug: Those who participated in another clinical study within 6 months before the time of screening shall be excluded.
- Medical device: Those who participated in a noninvasive clinical study may participate in this clinical study if the principal investigator determines that the safety or pharmacodynamic assessment will not be affected.

20) Individuals who have shown significant adverse events such as hypersensitivity reactions to the investigational product
21) Pregnant or breastfeeding females
22) Other individuals determined ineligible by the principal investigator to participate in the clinical study due to other reasons including clinical laboratory test results

1.4 Number of Subjects

1.4.1 Target Number of Subjects and Rationale for Calculation

Using this investigational product, clinical studies have been conducted on six diseases in total since 2007. Although there were no cases in which the drug was applied to CMT1A patients, a total of 18 subjects were recruited in a clinical study on amyotrophic lateral sclerosis among these studies. As a result of assessing safety, it was intended that this clinical study be conducted with 12 subjects considering the addition of indication and the slow progression of disease even though this clinical study also targets similar symptoms.

2. Establishment of Analysis Set

Efficacy assessment shall use the intention-to-treat (ITT) populations as the analysis sets, and analysis shall be performed on the auxiliary per-protocol (PP) sets. The definition of each analysis set for the assessment of safety, tolerability, and efficacy is as follows:

2.1 Analysis Sets for Safety and Tolerability Assessments

2.1.1 Safety Set

Among all subjects evaluated for their eligibility during the screening period, those subjects whose safety can be assessed after being administered the investigational product shall be included in the safety analysis. The subjects included in the safety analysis shall be analyzed based on the information of the actually administered investigational product. In addition, the demographic data (sex, age, etc.) and background factors (medical history, previous drug treatment history, etc.) shall be analyzed in the safety set.

2.2 Analysis Set for Efficacy Assessment

2.2.1 Intention to treat (ITT) Set

Subjects who have been administered the investigational product and have undergone efficacy assessment at least once shall be included in the ITT analysis set, regardless of protocol violations, compliance with visit schedule, etc.

2.2.2 Per Protocol Set (PPS)

PPS shall include those subjects in the ITT set who have completed the clinical study according to the clinical study protocol without major protocol violations. Subjects who fall under the following shall be defined as PPS.
The violation of eligibility in condition number ① of PPS shall be determined in a data review meeting prior to datalock.

① Subjects who have not violated the inclusion and exclusion criteria (eligible patients)
② Subjects who have completed all visits

Analysis shall also be performed on PPS by using the auxiliary analysis sets to analyze the sensitivity of the efficacy assessment.

2.3 Subgroup Analysis Population

When conducting assesments for adverse event and efficacy subgroup analysis shall be performed by considering the following items:

- Sex (male, female)
- Age (≤ median, > median)
- Baseline BMI (≤ median, > median)
- Presence or absence of medical history
- Presence or absence of concomitant drugs
- Disease severity (CMTNS-v2) (mild, moderate)

If the subjects within each subgroup are ≤ 30%, analysis shall not be performed. For example, if ≤ 30% of the total number of subjects is male, no subgroup analysis for sex shall be performed, and whether an analysis should be performed shall be determined in a data review meeting prior to datalock.

2.4 Data Review Meeting

The planned analyses shall be established in a data review meeting prior to datalock and the analysis sets shall be finally determined.
Based on the clinical study protocol, SAP, and the major protocol deviation items that occurred during the clinical study which were received from PM, the details of the criteria for analysis set definition shall be prepared as a Definition of Analysis Population (DAP) document. The major deviations considered in the final DAP shall be discussed in the data review meeting and the analysis sets shall be finally determined. The records on the details discussed in the data review meeting prior to datalock shall be collected and a blind data review report shall be prepared.

3. Definitions of Statistical Analysis Variables

3.1 Demographic Information and Comparison of Clinical Characteristics

3.1.1 Demographic Information

Sex, age, height, weight, BMI, smoking history, alcohol consumption history

3.1.2 Medical History Survey (past medical history, current illness)

Medical records on the medical history within 6 months before Visit 1 (screening) were obtained, and all positive/negative results were recorded in detail in the case report form. However, medical history/treatment history related to cancer was surveyed regardless of the time period. New results found at Visit 1 (screening) and Visit 2 (before administration of investigational product) were considered a part of medical history and were not recorded as adverse events. The investigator verified whether the diagnosis of CMT1A has been genetically confirmed for the patient. In the case of medical history, it shall be deemed as past medical history if persistence is "no," and if persistence is "yes," it shall be deemed as current illness.

3.1.3 Previous/Concomitant Medications (Treatment)

All medications and treatments administered within 6 months before Visit 1 (screening) were surveyed. Previous medications and previous treatments shall be defined as all previously collected medications and treatments before Visit 2*. Concomitant medications and treatments** shall refer to all medications that have been administered at least once starting from Visit 2 and throughout the clinical study. The categories of collected medications and treatments shall follow this definition. The following were also surveyed for each medication:

*Prior medications and prior treatments: Start date ≤ Visit 2 (Day 0)
**Concomitant medications and concomitant treatments: End date ≥ Visit 2 (Day 0) or if ongoing

- Brand name
- Indications for medication administration (reason for administration)
- Dose/strength, administration route, number of administrations
- Start and discontinuation dates of administration (whether to continue when the clinical study is terminated)

3.1.4 Physical Examination

This was performed at Visit 1 (screening), and physical examinations were performed on external appearance, skin, head/neck, chest/lungs, heart, abdomen, urinary/reproductive system, limbs, musculoskeletal system, nervous

system, lymph nodes, and other items. All abnormal findings were recorded in the case report form, and the clinical significance of each finding was assessed.

3.1.5 Electrocardiogram

A 12-lead electrocardiogram was performed at Visit 1 (screening). If there are results from a test performed at the same institution within 4 weeks before Visit 1 (screening), they may serve as a substitute.

3.2 Safety and Tolerability Endpoints

(1) Adverse events

Adverse events refer to undesirable and unintentional symptoms (e.g., motion sickness), signs (e.g., enlarged liver), and clinically significant abnormalities (e.g., abnormal laboratory test values), but they do not necessarily must have a causal relationship to the formulation used in the relevant clinical study.

Adverse Drug Reactions (ADRs)

Adverse drug reactions (ADRs) are all harmful and unintentional reactions that occur at any dose of the investigational product, and they refer to cases of which the causal relationship to the investigational product cannot be denied.

Adverse Events of Special Interest (AESIs)

AESIs are clinically significant unexpected medical reactions known to have been caused by the investigational product, or deemed to be possible risks based on the knowledge regarding the content and/or interactions of the investigational product.

All AESIs that occurred during the clinical study shall be collected in the case report form, and the events described below shall be classified as adverse events of special interest and shall be managed as safety data by the Helixmith PV team.

1) Coronavirus infection (COVID-19)
2) Local skin reactions (injection site reactions) after administration

Serious Adverse Events (Serious AEs/ADRs)

"Serious adverse events/adverse drug reactions" (serious AEs/ADRs) refer to cases that correspond to any one of the following among the adverse events or adverse drug reactions that occur at any dose of the investigational product.

1) Death has occurred or a life-threatening situation has developed.
2) Hospitalization or prolongation of hospitalization is required.
3) Permanent or serious impairment and functional decline have developed.
4) Malformation or abnormality has occurred in a fetus.
5) Other than the cases in (1) to (4), cases in which drug dependence or abuse has occurred or cases in which other medically significant situations have occurred such as hematologic diseases

The above phrase, "life-threatening situation has developed," refers to an event in which a subject faces an immediate risk of death at the time of AE occurrence.

If a subject visits the emergency room and the duration of treatment exceeds 24 hours, it shall be deemed as satisfying the hospitalization criterion. It shall not be deemed an adverse event or serious adverse event if hospitalization is scheduled prior to the initial administration of the investigational product, or in the case of cosmetic surgery. Elective surgery in the absence of adverse events and its following hospitalization as well as admission to a nursing hospital for the purpose of convalescence shall not be deemed as serious adverse events. However, if hospitalization was not planned or is the result of an adverse event, it shall be deemed as a serious adverse event.

Other than the situations listed above, if situations considered to have medically significant effects on the subjects' safety and health status do occur, the determination on whether the situation corresponds to a

serious adverse event shall be made based on the medical judgments of the physician in charge and relevant specialists, and appropriate actions shall be taken accordingly.

Unexpected Adverse Events

These are adverse events that differ in terms of the pattern or risk level of the adverse drug reactions compared with available drug-related information such as the investigator's brochure or drug attachments, or those adverse events that are not specified. An expected situation refers to a case in which a previously manifested adverse event is observed when the investigational product is used, while not being accompanied by past medical history or concomitant medications, and the description of which is provided in the investigator's brochure.

Expected Adverse Events

These are adverse events that have been observed and confirmed in previous clinical studies as well as being described in the available drug-related information such as the investigator's brochure, clinical study protocol, or drug attachments, and even though they do not include cases that are accompanied by past medical history or concomitant medications, the cases in which expected adverse events are repeatedly occur over time due to a specific disease state.

(2) Laboratory tests (general hematology/ general blood chemistry/urinalysis tests)
The laboratory test items are as follows:

- General hematology
  : WBC, RBC, Hb, Hct, MCV, MCH, MCHC, PLT, ESR, MPV, differential count of WBC (Band neutrophil, Segmented neutrophil, Eosinophil, Basophil, Lymphocyte, Monocyte)
- General blood chemistry test
  : total protein, albumin, globulin, A/G ratio, cholesterol, total bilirubin, AST, ALT, fasting glucose, BUN, creatinine, estimated GFR, Ca2+, phosphate, Na+, K+, Cl-, CRP, triglyceride, HDL-cholesterol, LDL-cholesterol
- Urinalysis
  : Color, turbidity, specific gravity, pH, albumin, glucose, ketone, bilirubin, blood, urobilinogen, nitrite, leukocyte esterase, microscopy (RBC, WBC, casts)

(3) Vital signs
Vital signs including blood pressure (measurement was taken with the subject in a sitting position after resting for at least 10 minutes prior to measurement), temperature, heart rate per minute, and respiratory rate per minute were measured. The measurement results were recorded in the subjects' case report forms. This was performed at Visit 1 (screening) and throughout the clinical study every time a subject made a visit (on the drug administration days consisting of Visits 2, 3, 4, and 5, it was performed both prior to administration and 2 ± 1 hours after administration). However, if there is a subject with abnormal findings in the test at Visit 3 (Day 14), a follow-up test may be performed at Day 30 at the discretion of the principal investigator.

3.3 Efficacy Endpoints

(1) Severity of disease
This was measured using Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS-v2) and the functional disability scale (FDS).

CMTNS-v2

Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS-v2) is a measurement tool for evaluating the severity of disease. Measurements shall be taken for 9 items which include 3 items for disease symptoms, 4 items for signs, and 2 items for neurophysiological testing. The severity of disease shall be classified according to scores as mild (≤10), moderate (11 to 20), and severe (>20). This clinical study shall target mild to moderate patients. This was performed at Visit 1 (screening), Visit 2 (Day 0), and Visit 7 (termination visit, Day 270) (performed prior to administration at Visit 2 [Day 0]).

FDS

The functional disability scale (FDS) assessed a patient from 0 to 8 points as shown below depending on the patient's mobility. The assessment day was at Visit 2 (Day 0), Visit 4 (Day 90), Visit 6 (Day 180), and Visit 7 (termination visit, Day 270) (assessment was performed prior to administration at Visit 2 [Day 0] and Visit 4 [Day 90]).

0=normal;
1=cramps and fatigability;
2=inability to run;
3=possible unaided;
4=with cane;
5=with crutch;
6=with walker;
7=wheelchair;
8=bedridden.

(2) Lower limb function

Changes in lower limb function were assessed using the overall neuropathy limitation score (ONLS) and the 10-meter walk test (10MWT).

ONLS leg scale

The overall neuropathy limitation scale (ONLS) is a tool for measuring the activity level of patients with peripheral neuropathy. It is scored by separately categorizing arms and legs. Measurement shall be performed only on legs in this clinical study. The measurement day was at Visit 2 (Day 0), Visit 4 (Day 90), Visit 6 (Day 180), and Visit 7 (termination visit, Day 270) (measurement was performed prior to administration at Visit 2 [Day 0] and Visit 4 [Day 90]).

10MWT

This is a test that measures the time required for a subject to walk 10 meters. A subject shall be made to walk at a desired speed while wearing shoes. The subject shall be allowed to use an assistive device that the subject normally uses, if any. The subject shall be made to walk a corridor that is 14 meters long, and the time taken to walk 10 meters shall be measured with a stopwatch provided by the sponsor (time taken to pass 10 meters excluding 2 meters each for the starting and ending portions). The assessment day was at Visit 2 (Day 0), Visit 4 (Day 90), Visit 6 (Day 180), and Visit 7 (termination visit, Day 270). (Assessment was performed prior to administration at Visit 2 [Day 0] and Visit 4 [Day 90]). The starting point at 2 meters, the point for ending measurement at 12 meters, and the point for end of walking at 14 meters shall be marked in advance along the corridor.

(3) Fatty infiltration level of lower limb muscles

The fatty infiltration level of the leg muscles injected with the investigational product shall be assessed with an MRI leg scan.

MRI leg

The muscles of lower limbs were imaged, and the fatty infiltration level of the leg muscles injected with the investigational product were measured and evaluated as fat content value (%) at one level for each muscle. The test days were at Visit 2 (Day 0) and Visit 7 (termination visit, Day 270) (performed prior to administration at Visit 2 [Day 0]). Considering the schedule, etc., of the institution, it was performed optionally at the early termination visit and unscheduled visits, and the details including the reasons for not performing the test were recorded in the case report form.

(4) Nerve regeneration potential

Nerve conduction studies including compound motor nerve action potential (CMAP), compound sensory nerve action potential (SNAP), and nerve conduction velocity (NCV) were performed.

The test days were at Visit 2 (Day 0) and Visit 7 (termination visit, Day 270) (performed prior to administration at Visit 2 [Day 0]).

(5) HGF antibody production by Engensis (VM202)
The presence or absence of HGF antibody (anti-HGF Ab) in blood was verified with the ELISA method. A preliminary assessment was performed on whether antibody production is correlated between the subject group determined to have increased muscle mass and improved function, and the subject group not determined as such.
However, if antibodies in blood were not produced in any of the subjects, the results were not presented.

The antibody test for hepatocyte growth factor was performed at Visit 2 (Day 0) and Visit 7 (termination visit, Day 270) (performed prior to administration at Visit 2 [Day 0]).

4. Statistical Analysis Method

4.1 General Principles of Statistical Analysis

Since this is a phase 1/2a clinical study and the number of subjects is small, the data from the treatment period and the follow-up period shall be descriptively compared and reviewed. For continuous data, descriptive statistics (number of subjects, mean, standard deviation, median, maximum, minimum) shall be presented, while frequencies and percentages shall be presented for categorical data.
If necessary or if comparisons are possible, statistical test shall be performed. The p-value shall be presented up to 4 decimal places, and a two-tailed test shall be performed under a significance level of 0.05. In addition, for descriptive statistics, numbers with values below the decimal point shall be presented up to 2 decimal places.

4.2 Adjustment for Covariates

Not applicable.

4.3 Handling of Dropouts or Missing Values

For missing values due to early termination of subjects, they shall not be imputed and shall be analyzed using the available data set.

Replacements shall be made as shown below if the start date and end date, start date/surgery date, and onset date and recovery date are not collected for prior/concomitant medications (treatment), medical history, and adverse events, respectively. However, if "year" is missing, the date shall not be replaced and shall be handled as a missing value.

Table 1. Handling of missing date values

	Missing	Handling of Missing Value	Exceptions
Start Date	If only "day" is missing	Replace with 01 (1st day).	If the corresponding date started in the same year and month of Day 0 (first administration day), set it as Day 0.
	If "day / month" are missing	01 (1st day) / JAN (January)	If the corresponding date started in the same year of Day 0 (first administration day), set it as Day 0.
End Date	If only "day" is missing	Replace with the last day of the corresponding month	If the end date handled as a missing value falls after the study termination date or before the study start date, set it as the study termination date.
	If "day / month" are missing	31 (31st day) / DEC (December)	

4.4 Multiple Comparisons or Multiplicity of Tests

Not applicable.

4.5 Subject Recruitment Status

4.5.1 Participation Status of Clinical Study and Dropout Subjects

The screening status and reasons for screening failure shall be presented for the recruited subjects, and the number of subjects shall be presented for the enrollment status in the clinical study. The number of subjects and percentages shall be summarized and presented for the clinical study completion and drop-out status, and a list shall be presented for the subjects dropped out. At this time, the screening status and the reasons for screening failure shall be shown in a schematic diagram.

4.5.2 Status of Analysis Set

The number of subjects and percentages shall be summarized and presented for the inclusion status of the analysis set and the reasons for exclusion.

4.5.3 Protocol Deviations

For subjects who completed the clinical study but were excluded from the analysis set due to protocol violations, the reasons for violation shall be presented as a list.

- Major protocol deviations shall be presented based on the ITT set.
- Major protocol deviations related to COVID-19 shall also be presented based on the ITT set.

4.6 Demographic Information and Comparison of Clinical Characteristics

4.6.1 Demographic Information

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) shall be presented for continuous variables (age, height, weight, BMI), while frequencies and percentages shall be presented for categorical variables (sex, smoking history, alcohol consumption history).

4.6.2 Medical History Survey (past medical history/current illness)

The number of subjects, percentages, 95% confidence interval (Clopper-Pearson Confidence Interval), and number of cases with past medical history and current illness shall be presented. In addition, past medical history and current illness shall be classified with the system organ classes (SOCs) and preferred terms (PTs) according to the medical dictionary for regulatory activities (MedDRA, V24.0), and the number of subjects, percentages, and number of cases shall be presented.

4.6.3 Previous/Concomitant Medications (Treatment)

The number of subjects, percentages, 95% confidence interval (Clopper-Pearson Confidence Interval), and number of cases shall be presented for prior and concomitant medications. In addition, the number of subjects, percentages, and number of cases shall be presented for prior and concomitant medications by classifying into anatomical main groups and therapeutic subgroups according to the ATC code (Anatomical Therapeutic Chemical classification System, 2021) of the WHO Drug Dictionary.

The number of subjects, percentages, 95% confidence interval (Clopper-Pearson Confidence Interval), and number of cases shall be presented for prior and concomitant treatments. In addition, prior and concomitant treatments shall be classified with the system organ classes (SOCs) and preferred terms (PTs) according to the medical dictionary for regulatory activities (MedDRA, V24.0), and the number of subjects, percentages, and number of cases shall be presented.

4.6.4 Physical Examination

For each physical examination item of the subjects, the frequencies and percentages shall be presented for clinically significant abnormalities (Normal / NCS [Not Clinically Significant Abnormal] / CS [Clinically Significant Abnormal]). In addition, a detailed list shall be presented for clinically significant abnormal results (CS) from physical examinations.

4.6.5 Electrocardiogram

For the electrocardiogram of the subjects, the frequencies and percentages shall be presented for clinically significant abnormalities (Normal / NCS [Not Clinically Significant Abnormal] / CS [Clinically Significant Abnormal]). In addition, a detailed list shall be presented for clinically significant abnormal results (CS) from electrocardiograms.

4.7 Safety and Tolerability Assessments

(1) Adverse events

Summarization and analysis of adverse events shall be performed on treatment-emergent adverse events (TEAEs).

The number of subjects, percentages, 95% confidence interval (Clopper-Pearson Confidence Interval), and number of cases shall be presented for treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), adverse events of special interest (AESIs), and serious adverse events/adverse drug reactions (SAEs). In addition, the number of subjects, incidence, and number of cases shall be presented for SAE status of adverse events, SAE reason, severity, causal relationship to the investigational product, relationship to the IP administration procedure, relationship to underlying disease, actions related to the investigational product, corrective treatments, outcomes, etc.

The adverse events, adverse drug reactions, and serious adverse events shall be encoded using the system organ classes (SOCs) and preferred terms (PTs) by using the medical dictionary for regulatory activities (MedDRA, V24.0). The number of subjects with onset, the incidence, the number of cases, etc., shall be presented for the encoded adverse events. In addition, a detailed list shall be presented if serious adverse events occur.

(2) Laboratory tests (hematology/ blood chemistry/urinalysis tests)

Laboratory tests shall present descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) for the quantity of change at each visit (DAY 14, DAY 90, DAY 104, DAY 180, DAY 270) compared with the measurement values of each visit and the baseline (DAY 0). The difference at each visit compared with the baseline shall be analyzed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy normality).

The rate of change for the clinically significant abnormalities (Normal / NCS [Not Clinically Significant Abnormal] / CS [Clinically Significant Abnormal]) at each visit (DAY 14, DAY 90, DAY 104, DAY 180, DAY 270) compared with the baseline (DAY 0) shall be summarized as frequencies and percentages and presented as a contingency table. The difference at each visit compared with the baseline shall be analyzed using the McNemar-Bowker's test. In addition, a detailed list shall be presented for clinically significant abnormal results.

(3) Vital signs

Vital signs shall present descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) for the quantity of change prior to administration at each visit (DAY 14, DAY 90, DAY 104, DAY 180, DAY 270) compared with the measurement values prior to administration at each visit and the baseline (DAY 0). The difference at each visit compared with the baseline prior to administration shall be analyzed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy normality).

The rate of change for the clinically significant abnormalities (Normal / NCS [Not Clinically Significant Abnormal] / CS [Clinically Significant Abnormal]) at each visit (DAY 14, DAY 90, DAY 104, DAY 180, DAY 270) compared with the baseline (DAY 0) prior to administration shall be summarized as frequencies and percentages and

presented as a contingency table. The difference at each visit compared with the baseline prior to administration shall be analyzed using the McNemar-Bowker's test.

In addition, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) shall be presented for the pre-/post-administration measurement values at each visit and the quantity of change for pre-administration versus post-administration. The differences between pre-administration and post-administration shall be analyzed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy normality).

The rate of change for the clinically significant abnormalities (Normal / NCS [Not Clinically Significant Abnormal] / CS [Clinically Significant Abnormal]) of pre-administration versus post-administration shall be summarized as frequencies and percentages and presented as a contingency table. The differences between pre-administration and post-administration shall be analyzed using the McNemar-Bowker's test.

A detailed list shall be presented for clinically significant abnormal results.

4.8 Efficacy Assessment

(1) Severity of disease
: The descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) for each item of CMTNS-v2 at the termination visit (DAY 270) compared with the baseline (DAY 0) shall be presented, and the differences at the termination visit compared with the baseline shall be analyzed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy the assumption of normal distribution). In addition, descriptive statistics (frequency, percentage) shall be presented for changes in the total score, and a contingency table shall be prepared for the pre-/post-administration differences, and analysis shall be performed using the McNemar-Bowker's test.

In addition, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) shall be presented for the changes in FDS at each visit (DAY 90, DAY 180, DAY 270) compared with the baseline (DAY 0), and analysis shall be performed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy the assumption of normal distribution) for the differences at each visit compared with the baseline.

(2) Lower limb function
: Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) shall be presented for the changes in lower limb function (ONLS leg scale, 10MWT)) at each visit (DAY 90, DAY 180, DAY 270) compared with the baseline (DAY 0), and analysis shall be performed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy the assumption of normal distribution) for the differences at each visit compared with the baseline.

(3) Fatty infiltration level of lower limb muscles
: Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) shall be presented for the changes in the level of fatty infiltration of lower limb muscles at the termination visit (DAY 270) compared with the baseline (DAY 0), and analysis shall be performed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy the assumption of normal distribution) for the differences at the termination visit compared with the baseline.

(4) Nerve regeneration potential
: Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) shall be presented for the changes in nerve conduction studies (CMAP, SNAP, NCV) at the termination visit (DAY 270) compared with the baseline (DAY 0), and analysis shall be performed using a paired t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy the assumption of normal distribution) for the differences at the termination visit compared with the baseline.

(5) HGF antibody generation by VM202

: Descriptive statistics (frequency, percentage) shall be presented for the HGF antibody production at the termination visit (DAY 270) compared with the baseline (DAY 0). A contingency table shall be prepared for the differences at the termination visit compared with the baseline, and analysis shall be performed using the McNemar's test.

4.9 Analysis of Other Groups

When conducting adverse event and efficacy assessments, subgroup analysis shall be performed by considering the items shown below.

If necessary, tests shall be performed on the differences between groups, and in the case of continuous data, analysis shall be performed using a two sample t-test (Wilcoxon's signed rank test if Shapiro-Wilk test results do not satisfy the assumption of normal distribution), while the Pearson's Chi-square test (Fisher's exact test if cells with expected frequency < 5 exceeds 20%) shall be used for categorical data.

- Sex (male, female)
- Age (≤ median, > median)
- Baseline BMI (≤ median, > median)
- Presence or absence of medical history
- Presence or absence of concomitant drugs
- Disease severity (CMTNS-v2) (mild, moderate)

If the subjects within each subgroup are ≤ 30%, analysis shall not be performed. For example, if ≤ 30% of the total number of subjects is male, no subgroup analysis for sex shall be performed, and whether an analysis should be performed shall be determined in a data review meeting prior to datalock.

[redacted]