HELIXMITH

Protocol Title:	**A 6-Month Extension Study Following Protocol VMALS-002-2 (A Phase 2a, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety of Engensis in Participants with Amyotrophic Lateral Sclerosis)**
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DISCLOSURE STATEMENT

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1. PROTOCOL SUMMARY

The following sections present an overview of the study, study schema, and Schedule of Activities (SoA). A list of abbreviations is presented in Section 10.3, Appendix 3.

1.1. Synopsis

Protocol Title: A 6-Month Extension Study Following Protocol VMALS-002-2 (A Phase 2a, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety of Engensis in Participants with Amyotrophic Lateral Sclerosis)

Short Title: A 6-Month Extension Study to Assess the Safety of Engensis in Amyotrophic Lateral Sclerosis

Rationale:

The purpose of this study is to evaluate the long-term safety of intramuscular (IM) administration of Engensis in Participants with Amyotrophic Lateral Sclerosis (ALS) who were previously randomized, received treatment, and completed the Day 180 Visit of Study VMALS-002-2. Safety will be assessed by incidences of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and the clinically significant laboratory values. See the table below for additional, exploratory endpoints.

Engensis contains the active pharmaceutical ingredient VM202, a novel genomic complementary deoxyribonucleic acid (cDNA) hybrid human hepatocyte growth factor (HGF) coding sequence (HGF-X7) expressing two isoforms of HGF, HGF_{728} and HGF_{723}, being developed by Helixmith for treatment of ALS.

Data from Helixmith's first clinical trial in ALS, the Phase 1/2 study (VMALS-001) that included 18 Participants who were followed for 9 months, suggested that targeted delivery of HGF to motor neurons via intramuscular (IM) injections of Engensis was safe and well-tolerated. Safety assessments during the study included reports of 79 adverse events (AEs) in 17 Participants (94.4%), including 26 mild injection site reactions (Grade 1). Five SAEs were reported in 3 Participants. Only an injection site reaction was considered related to study treatment. Following injections until Day 90, a plateau or a relative slowing in the decline of the Revised Amyotrophic Lateral Sclerosis Function Rating (ALSFRS-R) scores and muscle strength was noted, suggesting a slowing of disease progression. After 90 days, the plateau was no longer observed in the ALSFRS-R, with the notable exception of a trend toward better preservation of bulbar and breathing functions as measured by the ALSFRS-R.

Data for Participants at study visits in Study VMALS-002-2 will be used as reference points for changes in safety assessments during the extension study VMALS-002-2b.

Objectives and endpoints for this extension study are presented in the following table. Note that there will be no Engensis or Placebo treatments in VMALS-002-2b. Therefore, the comparisons

of Engensis to Placebo for long-term safety in VMALS-002-2b are based on the randomization of Participants and the treatments they received in VMALS-002-2 (Engensis or Placebo).

Objectives	Endpoints
Primary	
• To evaluate the long-term safety of intramuscular (IM) injections of Engensis in Participants with Amyotrophic Lateral Sclerosis (ALS)	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events of special interest (AESIs) for Engensis compared to Placebo • Incidence of clinically significant laboratory values for Engensis compared to Placebo
Exploratory	
• To evaluate changes in muscle function following Engensis injections in ALS Participants	• Change from Baseline (Study VMALS-002-2 Day 0) in total mean Revised Amyotrophic Lateral Sclerosis Function Rating (ALSFRS-R) scores at Day 365 for Engensis compared to Placebo • Change from Baseline (Study VMALS-002-2 Day 0) in ALSFRS-R subscores for Fine and Gross Motor Functions (sum of scores for items 4 to 9) and for Bulbar Function (sum of scores for items 1 to 3) at Day 365 for Engensis compared to Placebo • Changes in the slope of the total ALSFRS-R score over time for Engensis compared to Placebo
• To evaluate muscle strength changes following Engensis injections in ALS Participants	• Change from Baseline (Study VMALS-002-2 Day 0) in muscle strength assessed bilaterally by Handheld Dynamometry (HHD) in muscles in the upper and lower extremities at Day 365 for Engensis compared to Placebo

Objectives	Endpoints
• To determine whether IM administration of Engensis has effects on respiratory function in ALS Participants	• Change from Baseline (Study VMALS-002-2 Day 0) in Slow Vital Capacity (SVC) at Day 365 for Engensis compared to Placebo • Time to tracheostomy for Engensis
• To determine whether IM administration of Engensis has positive effects on survival in ALS Participants	• Time to all-cause mortality compared to Placebo
• To evaluate Quality of Life improvement following Engensis injections in ALS Participants compared to Placebo	• Change from Baseline (Day 0) in Quality of Life (QoL) using the ALS Assessment Questionnaire (ALSAQ; with 40 items, ALSAQ 40) on Day 365 for Engensis compared to Placebo
• To evaluate Patient and Clinical Reported Outcome improvement following Engensis injections in ALS Participants compared to Placebo	• Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) at Day 365 for Engensis compared to Placebo

Overall Design

VMALS-002-02b is a Phase 2a, 6-month extension study, multicenter study designed to assess the long-term safety of Engensis (containing the active pharmaceutical ingredient VM202) in Participants with ALS.

Participants will be enrolled in the VMALS-002-2b study following the completion of the Day 180 Visit of Study VMALS-002-2. Participants will continue to be identified by the same Participant number.

Assessments to be conducted during this VMALS-002-2b extension study are as follows: vital signs; weight and height; complete physical examination; a record of all concomitant medications and procedures; ALSFRS-R; Handheld Dynamometry (HHD); Slow Vital Capacity (SVC); Amyotrophic Lateral Sclerosis Assessment Questionnaire, 40 questions (ALSAQ-40); Patient Global Impression of Change (PGIC); Clinical Global Impression of Change (CGIC); and urine pregnancy test for females of childbearing potential. Assessments of TEAEs, TESAEs, AESIs, and clinically significant laboratory values will continue from the Day 180 Visit of Study VMALS-002-2 throughout the VMALS-002-2b extension study, to Day 365.

Study and Treatment Duration:

There will be no treatments during this extension study. The timing for visits in the VMALS-002-2b study starts at the conclusion of the Day 180 Visit in VMALS-002-2. Participants in VMALS-002-2b will be followed for 180 days to Day 365.

Visit Frequency:

Consented Participants will be seen and evaluated for safety at visits every 60 days (Days 240, 300, and 365/ET).

Intervention Groups and Duration:

There will be no Engensis treatments administered during this 180-day extension study.

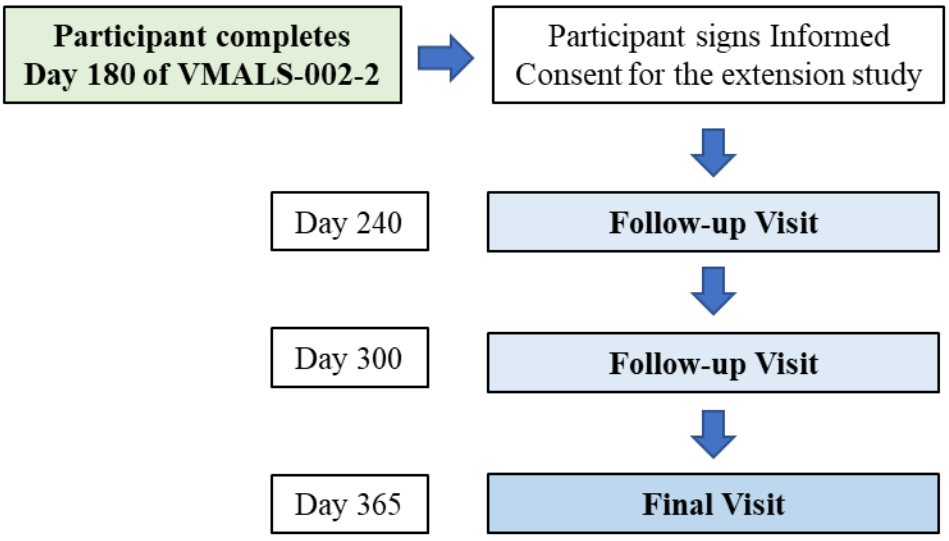
Number of Participants:

The number of Participants to be enrolled in this extension study depends upon the number of subjects who complete the Day 180 Visit in VMALS-002-2 (prior to, during, or after their Day 180 Visit) and who provide written informed consent. The maximum potential Participants in VMALS-002-2b is 18, based on enrollment in VMALS-002-2.

Data Safety Monitoring Board:

An independent Data Safety Monitoring Board (DSMB) will periodically review a limited set of unblinded (noncomparative) tables and/or listings, including all reported TEAEs, TESAEs, and AESIs.

1.2. Study Schema



1.3. Schedule of Activities (SoA)

		Day 240	Day 300	Day 365/ET
	Visit Window (days):	± 7	± 7	± 7
Procedure				
1	Informed Consent (obtained prior, during or after the Participant's Day 180 Visit in Study VMALS-002-2)			
2	Vital Signs, Weight, Height	X	X	X
3	Complete Physical Examination	X		X
4	12-Lead ECG	X		X
5	Serum Chemistry, Hematology	X		X
6	Concomitant Medications and Procedures	X	X	X
7	Urine Pregnancy Test			X
8	SVC	X	X	X
9	ALSFRS-R	X	X	X
10	HHD	X	X	X
11	ALSAQ-40	X		X
12	PGIC and CGIC	X		X
13	TEAEs, TESAEs	←	—	→
14	AESIs	←	—	→

FOOTNOTES FOR THE SCHEDULE OF ACTIVITIES

Note: The **Schedule of Activities** includes activities during all Study Visits.

Order of Assessments during Visits (if assessment is to be performed): AEs/TEAEs, SAEs/TESAEs, vital signs and weight, ALSFRS-R, HHD, ALSAQ-40, pregnancy test, complete physical exam, SVC, 12-Lead ECG, concomitant medications and procedures, PGIC and CGIC, and blood sample collection for laboratory assessments (serum chemistry and hematology)

Abbreviations: AESI = adverse events of special interest; ALSAQ-40 = Amyotrophic Lateral Sclerosis Assessment Questionnaire, 40 questions; ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; CGIC = Clinical Global Impression of Change; Day 365/ET = Day 365 Visit or Early Termination; ECG = electrocardiogram; ET = early termination or withdrawal; HHD = Handheld Dynamometry; PGIC = Patient Global Impression of Change; SVC = Slow Vital Capacity; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

1. **Informed Consent** process is to be obtained prior to, during or after the Participant's Day 180 Visit in Study VMALS-002-2
2. **Vital Signs, Weight, and Height:** Vital signs and weight will be measured at Study Visits on Days 240, 300, and 365/ET (Day 365 or Early Termination). After the Participant has rested in the seated position for 5 minutes, vital signs will be collected, including temperature, sitting blood pressure, heart rate, respiratory rate, and oxygen saturation on room air. The method of temperature measurement should be according to the Site's policy and should be consistently applied.

3. **Complete Physical Examination** will be performed on Days 240 and 365/ET. The examination will include the following: an examination of the skin/integumentary systems, general appearance, head, neck (including thyroid), eyes, ears, nose, throat, lymph nodes, chest (lungs), heart, abdomen, musculoskeletal system, neurological system, and any additional assessments needed to establish Baseline status or evaluate symptoms or TEAEs. Any abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and the abnormalities should be recorded as TEAEs, TESAEs, or AESIs.
4. **12-Lead Electrocardiogram (ECG)** will be performed at Days 240 and 365/ET. Clinically significant abnormalities are to be recorded as adverse events. The ECG recording must be stored with the Participant's records.
5. **Serum Chemistry and Hematology:** Blood samples will be collected for serum chemistry and hematology assessments on Days 240 and 365/ET. Test results will be reviewed and assessed by the Investigator for clinically significant abnormal laboratory findings, which should be recorded as TEAEs, TESAEs, and AESIs.

   Chemistry includes sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate, magnesium, glucose, amylase, lipase, creatine kinase, lactate dehydrogenase, and:

   a. Kidney function tests (blood urea nitrogen, creatinine)
   b. Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, gamma-glutamyl transpeptidase [GGT], total bilirubin, total protein, and albumin)

   Hematology includes platelet count, hemoglobin, hematocrit, white blood cell count, and neutrophil count
6. **Concomitant Medications and Procedures** will be recorded on Days 240, 300, and 365/ET, and will include all medications or vaccines, including over-the-counter or prescription medicines, vitamins, herbal supplements, and procedures that the Participant was received. For each medication, treatment, or procedure, the following information will be collected: Medication trade or generic name, type of procedure, indication, start date, stop date or ongoing, dose, units, frequency, and route of administration.
7. **Urine Pregnancy Test** will be conducted for women of childbearing potential on Day 365/ET.
8. **Slow Vital Capacity (SVC)** will be measured on Days 240, 300, and 365/ET.
9. **ALSFRS-R**: **Revised Amyotrophic Lateral Sclerosis Functional Rating Scale** will be performed on Days 240, 300, and 365.
10. **Handheld Dynamometry (HHD)** will be measured on Days 240, 300, and 365/ET:
11. **ALSAQ-40**: **Amyotrophic Lateral Sclerosis Assessment Questionnaire, 40 questions (ALSAQ-40)** will be measured on Days 240 and 365/ET.
12. **Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC)** will be conducted on Days 240 and 365/ET.
13. **Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs):** TEAEs/TESAEs will be recorded after informed consent on Day 180 of VMALS-002-02 for Participants in VMALS-002-2b. All TESAEs during this extension study will be recorded and reported to the Sponsor/designee within 24 hours of awareness of the TESAE by the Site.
14. **Adverse Events of Special Interest (AESIs):** All AESIs will be continuously monitored throughout the study.

2. INTRODUCTION

Engensis is a novel gene therapy being developed for treatment of ALS. The active pharmaceutical ingredient of Engensis is VM202, a plasmid deoxyribonucleic acid (DNA) designed as a gene transfer method to simultaneously express two isoforms of human hepatocyte growth factor (HGF), HGF_{728} and HGF_{723}, which are identical to wild-type human forms.

Hepatocyte growth factor is a potent angiogenic and vasculogenic growth factor stimulating the growth of endothelial cells and migration of vascular smooth muscle cells. As a multifunctional mesenchyme-derived cytokine, it has potent angiogenic and anti-apoptotic effects, including that of the lymphatic system. In addition, HGF upregulates the expression of vascular endothelial growth factor (VEGF) and other factors and demonstrates greater mitogenic activity than that of VEGF alone in human aortic endothelial cells in vitro. HGF is also important in the pathophysiology of insulin resistance, as a neurotrophic factor promoting axonal growth and regeneration in diabetics in whom loss of microvasculature may accelerate neuronal loss, more so than exogenous VEGF (see the Investigator's Brochure [IB] for more detailed information).

2.1. Study Rationale

VMALS-002-2b is a safety extension of VMALS-002-2, a well-controlled study to evaluate the long-term safety of IM administration of Engensis to Participants with ALS.

2.2. Background

2.2.1. Pathophysiology of Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is an adult-onset neurodegenerative disorder characterized by the loss of upper and lower motor neurons. The disease is diverse in its presentation, cause, and progression, but in general, ALS presents clinically as asymmetric muscle weakness, wasting, spasticity, weight loss, dysphagia, and paralysis; in 10% to 15% of patients; cognitive impairment may arise before or following that of motor neuron dysfunction. Pathologically, ALS is characterized by progressive degeneration and loss of motor neurons in the spinal cord, brainstem, and cerebral cortex. From the time of diagnosis, median survival is 3 to 5 years; about 10% of patients can survive for ≥10 years. While most ALS cases are sporadic (primary or idiopathic), about 5% to 10% of patients have a positive family history (familial ALS),[1,2] with a mutation in the Cu/Zn superoxide dismutase 1 (SOD1) gene accounting for 10% of familial ALS.[3]

Estimates of the incidence of ALS worldwide range from 1 to 3 cases per 100,000 people annually, with a higher incidence in Caucasians,[4,5,6,7,8] in people who smoke,[9,10] and in several geographic regions in which environmental toxins are suspected.[11,12,13,14] The ALS Association, the Centers for Disease Control and Prevention, and the National Institute of Neurological

Disorders and Stroke estimate that as many as 30,000 Americans may have the disease at any given time, with approximately 5,600 newly diagnosed patients annually.*

Multiple mechanisms for the selective vulnerability, degeneration, and early dying-back axonopathy of motor neurons have been proposed and investigated. They include protein misfolding, mitochondrial dysfunction, oxidative damage, defective axonal transport, excitotoxicity, insufficient growth factor signaling, and inflammation.[15,16,17,18,19,20] Toxicity results from a combination of damage incurred directly within motor neurons and through damage incurred by non-neuronal neighbors, including astrocytes and microglia, whose actions amplify the initial damage and drive disease progression and spread. Microglia activate an inflammatory cascade via secretion of monocyte chemoattractant protein 1 (MCP-1) and other cytokines. Astrocytes contribute to neuron injury by releasing inflammatory mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2), reduced lactate release, activation of pro-NGF-p75 (nerve growth factor) receptor signaling and reduced activity of the glutamate reuptake transporter excitatory amino acid transporter 2 (EAAT2). Motor neurons might also undergo transcriptional dysregulation and abnormal ribonucleic acid (RNA) processing, which, together with overproduction of reactive oxygen species, contributes to aberrant protein folding. Aberrant proteins can form aggregates, leading to proteasome impairment and endoplasmic reticulum stress. The resulting mitochondrial impairment and dysregulation of calcium handling trigger autophagy and the apoptotic cascade.[21,22] The process is "contagious" and self-perpetuating, affecting the dynamics of cell death in neighboring cells due to release of interleukin-1β , tumor necrosis factor alpha (TNF-α), and free radicals.[23] Figure 1 depicts the molecular processes involved in motor neuron injury in ALS.

* http://www.alsa.org/about-als/who-gets-als.html (accessed October 12, 2015)
http://wwwn.cdc.gov/als/WhatisALS.aspx (accessed October 12, 2015)
http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_ALS.htm (accessed October 12, 2015)

[redacted]

[redacted]

[redacted]

[redacted]

and/or time to tracheostomy, without providing a statistically significant differences in muscle strength or neurological function.[30]

Edaravone was approved by the Food and Drug Administration (FDA) on May 5, 2017, for patients with ALS. The drug is administered intravenously and believed to reduce oxidative stress in the nervous system, a process that kills neurons in patients with ALS. Edaravone was approved based on the results of a Phase 3 clinical trial in Japan and South Korea in which 137 ALS patients were given either edaravone or placebo. The group given edaravone experienced a 33% reduction in the decline of their physical limitations compared with the placebo group. Statistical significance was only reached in Participants diagnosed less than two years earlier and with rapid progression of symptoms, however; 2 other Phase 3 studies failed to show any clinical benefit of edaravone, and survival was not demonstrated to be prolonged with its use.

Neither riluzole nor edaravone prevent or correct the underlying causes of ALS. Clearly, a therapy that could impede or reverse neurodegeneration is needed for patients with ALS. Engensis produces HGF, which acts as a neurotrophic factor that aids in the development and regeneration of peripheral nerves; it activates Schwann cells to become repair-type cells and enhances the remyelination process, consequently leading to the proper regeneration of injured peripheral nerves in animal models (see the IB for more information).

Treatment approaches based on anatomic delivery strategies have also been proposed for treatment of ALS or other neurodegenerative diseases.[31,32] For example, based on observations of retrograde neural transport of biotherapeutics following IM injection in animal models, a delivery approach of IM injections of stem cells has been applied in clinical trials of various adult stem cell populations, all with a limited number of injections and few muscle targets.[33,34,35] A much broader anatomic delivery strategy is being used for Engensis injections being evaluated in Helixmith clinical trials.

2.2.3. Hepatocyte Growth Factor for Treatment of Amyotrophic Lateral Sclerosis

Hepatocyte growth factor (HGF) is a multi-functional mesenchyme-derived cytokine. It is a recognized potent angiogenic growth factor and anti-apoptosis agent, stimulating the growth of endothelial cells and the migration of vascular smooth muscle cells.[36,37,38,39] HGF stimulates DNA, RNA, and protein synthesis by endothelial cells in a dose-dependent manner, upregulates VEGF expression, and exhibits greater mitogenic activity than that of VEGF alone in human aortic endothelial cells *in vitro*.[40,41,42]

Although largely thought of as an angiogenic agent, HGF has been recently identified as a neurotrophic factor.[43,44,45,46,47,48,49] HGF and its cognate receptor (the c-Met receptor) are expressed in the peripheral nervous system as well as in various regions of the brain and spinal cord. Sun *et al.* (2002) found that local sustained HGF production in neural tissue in SOD^{G93A} mice (transgenic ALS model) alleviated the symptoms of ALS by direct neurotrophic activities on motor neurons and indirect activities on glial cells.[47] They found that HGF was neuroprotective. SOD mice transfected with a single copy of the HGF gene (G93A/HGF) retained a significantly larger number of spinal motor neurons with a healthier morphology than SOD mice without the HGF gene (G93A single transgenic).

G93A/HGF mice also experienced improved motor performance, significantly delayed onset in paralysis, and survived longer than G93A mice. Researchers also found indirect evidence that HGF suppresses microgliosis (intense reaction of central nervous system [CNS] microglia to pathogenic insults) and astrocytosis (abnormal increase in the number of astrocytes), both of which contribute to motor neuron degeneration by producing cytotoxic cytokines and eventual glial scar formation.[50,51]

It has been demonstrated that HGF can promote neurogenesis, angiogenesis, and synaptogenesis and that it can inhibit fibrotic changes in ischemic regions better than glial cell line-derived neurotrophic factor (GDNF).[52]

HGF may also have protective effects against excitotoxic injuries, because it has been shown to attenuate axonal degeneration by reducing excitotoxicity through modulation of the expression of the scaffolding protein (members of the signaling cascade downstream of cell surface receptors) of the N-methyl-D-aspartate (NMDA) receptor at the synapse.[53,54]

Finally, HGF may stave off cell death and halt the cascade of neighboring cell damage by inhibiting caspase signaling directly in motor neurons and indirectly by its effects on astrocytes.[55] In ALS patients, chronic, sublethal activation of caspase appears to mediate cell dysfunction, which precedes cell death.[56,57] Cell dysfunction of substantial magnitude, occurring before cell death, might result in symptomatic disease. Given that caspases may be active in individual neurons for a long period (potentially weeks to months), inhibition of caspase in these circumstances could reduce cell dysfunction and delay cell death.[54] Therefore, the neurotrophic action of HGF on motor neurons is, at least in part, promoted by preventing caspase-mediated cell death signals.

HGF overexpression also attenuates monocyte chemoattractant protein-1 (MCP-1, one of the important chemokines that controls migration and infiltration of monocytes and macrophages during inflammation) induction in astrocytes, which results in a reduction in microglial accumulation, a hallmark inflammatory process in ALS.[58]

The challenge associated with delivering a targeted sustained dose of exogenous HGF is in overcoming the instability of HGF in blood circulation and its rapid clearance by the liver; HGF has an in vivo half-life of less than 15 minutes.[59,60]

One approach to increasing HGF available to neurons is to develop a gene transfer strategy that would allow for persistent expression of HGF protein in vivo. Although plasmid DNA is one of the least efficient gene transfer systems currently in use, the fact that it is associated with limited persistence and no propensity for genomic integration (particularly in skeletal muscle tissue) makes it an attractive option for local targeted delivery.

2.2.4. Engensis and VM202

The investigational agent (study drug) being studied in this protocol is Engensis, which contains the active pharmaceutical ingredient VM202. VM202 is a plasmid DNA that contains the novel genomic complementary DNA (cDNA) hybrid human HGF coding sequence (HGF-X7) expressing two isoforms of HGF, HGF_{728} and HGF_{723} (Figure 2).

[redacted]

proteins.

Figure 2: VM202 Construct

2.2.5. Nonclinical Data

The nonclinical safety of Engensis has been evaluated for general toxicity following single IM and intravenous doses in rats (up to 28 days) and following multiple intermittent (weekly or monthly) IM doses in rabbits and rats (up to 8 weeks; see the IB). The potential for genomic integration at the injection site as well as the potential for distribution to and persistence of VM202 in reproductive tissues was evaluated in rats. The ability of VM202 to induce humoral immune responses was evaluated following IM administration with or without adjuvant in mice. All species used for these studies (mouse, rat, and rabbit) were shown in in vivo experiments to be able to express the plasmid following IM injection.

Collectively, Engensis has been well-tolerated in all preclinical studies conducted to date, with the only evidence of toxicity consisting of mild, transient injection site irritation. No evidence of systemic toxicity has been noted in any nonclinical study, and human HGF was not detected in the sera of rats or rabbits following intramuscular injection (assay lower limit of quantitation [LLOQ] of 125 pg/mL). No evidence has been seen of genomic integration, potential germ cell transmission, or immunostimulatory effects following IM administration of Engensis to animals.

2.2.6. Clinical Data

Engensis has been or is being evaluated in 10 clinical studies in the US and/or Korea. These include two studies (Phases 1 and 2) in critical limb ischemia (CLI), one study in peripheral

artery disease (Phase 2), one study in coronary artery disease (Phase 1), four studies (Phase 1/2, Phase 2, and two Phase 3) in Participants with painful diabetic peripheral neuropathy (DPN), a study (Phase 1/2) in ALS, and one (Phase 3) study in diabetic Participants with chronic nonhealing foot ulcers (NHU). Engensis was well tolerated and the most frequent reaction was pain at injection sites in 1-4% of Participants, which was similar to that observed in the placebo groups. No systemic effects have been attributed to Engensis.

2.2.6.1. Phase 1/2 Study in Participants with Amyotrophic Lateral Sclerosis

A Phase 1/2, open label, single center study in 18 Participants diagnosed with clinically definite, clinically probable, or clinically probable-laboratory supported ALS (VMALS-001; NCT02039401) lasting 9 months was completed.[61] Prior to injections on Day 0, Participants were assessed using the ALSFRS-R, the Medical Research Council (MRC) scale for muscle strength testing, dynamometry, forced vital capacity (FVC), and muscle circumference of treated muscles.

All Participants (18 Participants) received a total of 64 mg of Engensis IM in the upper limbs (abductor pollicis brevis, first dorsal interosseous, biceps, deltoid, extensor carpi radialis, flexor carpi ulnaris, and flexor carpi radialis) and lower limbs (quadriceps, gastrocnemius, and tibialis anterior).

Engensis was administered over the course of four visits: Days 0, 7, 14, and 30. As in previous Engensis studies, the final dose of Engensis for each target muscle group was divided and administered 2 weeks apart with injection of the upper limbs at separate visits followed by injection of the lower limbs.

Post-injection, ALSFRS-R, FVC, and muscle strength (determined by the MRC scale) were assessed at Days 30, 60, and 90, and at 6 and 9 months. Muscle circumference and dynamometry were conducted on Days 60 and 90, and at 6 and 9 months. Participants were contacted through 36 months by phone to assess survival.

After Engensis or Placebo injections through Day 30, seventeen (17) Participants completed the 9-month follow-up; one Participant died prior to the 9-month visit. Three (3) Participants completed the study (36-month follow-up), while 14 Participants died following the 9-month visit; all deceased Participants died due to respiratory failure associated with ALS. Four additional serious adverse events (SAEs) that required hospitalization were reported. All deaths and SAEs were classified as unrelated to the study drug. Injection site reactions were limited to pain and/or bruising and none exceeded grade 2 severity.

2.2.6.2. Other Engensis Clinical Studies

See the IB for detailed presentation of results from all 10 clinical studies in the USA and Korea (see Section 2.2.6). Also, see Section 4.3 (Dose Justification) for descriptions of prior clinical studies with Engensis that contributed to the selection of doses and dosing regimen for this current study.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

The risks for the study medication and study procedures are summarized in the following table.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks of Engensis		
Cancer **Patients with melanoma and tongue cancer appear to be at an increased risk of death due to ALS**[62]	Angiogenesis plays an important role in the proliferation and metastatic spread of cancer as these processes are dependent on an adequate supply of oxygen and nutrients and removal of waste products.	Participants who develop any type of cancer during VMALS-002-2 will be followed long-term in VMALS-002-2b
Angiogenesis	Intimal angiogenesis in atherosclerotic plaques contributes to unstable plaque, plaque hemorrhage, and plaque rupture that predisposes to thrombotic or embolic events.	Participants who have experienced a stroke, cerebrovascular accident, or myocardial infarction within 3 months before Screening for VMALS-002-2 and Participants with peripheral artery disease (PAD) or PAD requiring revascularization will be excluded from VMALS-002-2b
Risks of Study Procedures		
Complications of venipuncture (for blood draws for laboratory tests)	Venipuncture complications include minor bruising, hypotension, and syncope.	Incidences of adverse events of bruising, hypotension, and syncope will be closely monitored throughout the study.

Adverse Events in Clinical Studies

Engensis has been well tolerated in all clinical studies conducted thus far in more than 500 Participants. The preponderant adverse events have consisted of mild, transient injection site effects, including itching, erythema, pain, and muscle spasms. Other TEAEs that have been reported were generally mild to moderate. Refer to the IB for a table of AEs that occurred in ≥ 2% of trial Participants.

Five SAEs have been reported to date as possibly related to study treatment:

- Colon cancer in the Phase 1 trial of CLI (assessed by the investigator to be possibly related to study drug and, even though the sponsor noted that the Participant had a history of colon polyps, a relationship to study drug could not be ruled out)
- Peroneal deep vein thrombosis (categorized as possibly related to the study injection) in the Phase 2 trial of CLI. The mechanism by which HGF or VM202 could be causative is not established.

SAEs reported as possibly related in the VMDN-003 trial included:

- Vitreous hemorrhage of the eye (categorized as possibly related to the study drug but was probably related to underlying disease)
- Myocardial infarction (categorized by Helixmith as possibly related to the study drug, although categorized by the investigator as not related to the study drug)
- Adenocarcinoma (categorized as possibly related to the study drug by the investigator and not related to the study drug by Helixmith)

2.3.2. Benefit Assessment

In ALS, sustained, local production of HGF in neural tissue may alleviate symptoms by direct neurotrophic and indirect neuroprotective activities on motor neurons. HGF has also been reported to play an important role in reversing or limiting muscle damage and muscular atrophy; exogenous treatment of HGF ameliorated skeletal muscle atrophy and increased the generation of new muscle fibers.

Engensis induces relatively rapid and prolonged production of HGF, which, through its multiple mechanisms of actions on microvascular and neural tissue repair, has the potential to improve outcomes in ALS patients, as suggested by preceding studies. If Engensis shows favorable outcomes in this study, it may be considered an important agent with a durable therapeutic effect for ALS patients.

2.3.3. Overall Benefit / Risk Conclusions

The overall profile of potential benefits and apparent safety for Engensis provide sufficient support to justify the conduct of the present extension study in its aim to meet the unmet needs of ALS patients.

3. OBJECTIVES AND ENDPOINTS

Objectives and endpoints for this extension study are presented in the following table. Note that there will be no Engensis or Placebo treatments in VMALS-002-2b. Therefore, the comparisons of Engensis to Placebo for long-term safety in VMALS-002-2b are based on the randomization of Participants and the treatments they received in VMALS-002-2 (Engensis or Placebo).

Objectives	Endpoints
Primary	
• To evaluate the long-term safety of intramuscular (IM) injections of Engensis in Participants with Amyotrophic Lateral Sclerosis (ALS)	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events of special interest (AESIs) for Engensis compared to Placebo • Incidence of clinically significant laboratory values for Engensis compared to Placebo
Exploratory	
• To evaluate changes in muscle function following Engensis injections in ALS Participants	• Change from Baseline (Study VMALS-002-2 Day 0) in total mean Revised Amyotrophic Lateral Sclerosis Function Rating (ALSFRS-R) scores at Day 365 for Engensis compared to Placebo • Change from Baseline (Study VMALS-002-2 Day 0) in ALSFRS-R subscores for Fine and Gross Motor Functions (sum of scores for items 4 to 9) and for Bulbar Function (sum of scores for items 1 to 3) at Day 365 for Engensis compared to Placebo • Changes in the slope of the total ALSFRS-R score over time for Engensis compared to Placebo

Objectives	Endpoints
• To evaluate muscle strength changes following Engensis injections in ALS Participants	• Change from Baseline (Study VMALS-002-2 Day 0) in muscle strength assessed bilaterally by Handheld Dynamometry (HHD) in muscles in the upper and lower extremities at Day 365 for Engensis compared to Placebo
• To determine whether IM administration of Engensis has effects on respiratory function in ALS Participants	• Change from Baseline (Study VMALS-002-2 Day 0) in Slow Vital Capacity (SVC) at Day 365 for Engensis compared to Placebo • Time to tracheostomy for Engensis
• To determine whether IM administration of Engensis has positive effects on survival in ALS Participants	• Time to all-cause mortality compared to Placebo
• To evaluate Quality of Life improvement following Engensis injections in ALS Participants compared to Placebo	• Change from Baseline (Day 0) in Quality of Life (QoL) using the ALS Assessment Questionnaire (ALSAQ; with 40 items, ALSAQ 40) on Day 365 for Engensis compared to Placebo
• To evaluate Patient and Clinical Reported Outcome improvement following Engensis injections in ALS Participants compared to Placebo	• Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) at Day 365 for Engensis compared to Placebo

4. STUDY DESIGN

4.1. Overall Design

VMALS-002-2b is a safety extension study following VMALS-002-2 (A Phase 2a, double-blind, randomized, placebo-controlled, multicenter study designed to assess the safety of IM administration of Engensis in Participants with ALS). Following completion of the Day 180 visit in VMALS-002-2 and signing of written informed consent, Participants may be enrolled in this approximately 180-day extension study.

4.2. Scientific Rationale for Study Design

VMALS-002-2b is designed as a safety extension study to evaluate the long-term safety profile of Engensis following the main study, VMALS-002-2, which is a well-controlled Phase 2a study in ALS Participants, as it is a double-blind, randomized, placebo-controlled, and multicenter study to evaluate muscle biomarkers and the safety profile of Engensis in Participants with ALS.

4.3. Justification for Dose

No treatments will be administered during this extension study.

4.4. Randomization

There is no randomization in this study.

4.5. End of Study Definition

The end of the study is defined as the date on which the last Participant in the study completes the Day 365 Visit, is terminated, or discontinued early from the study (early termination).

4.6. Study Completion

The study will be considered complete upon Helixmith's approval of the clinical study report.

4.7. Completed Participants

A Participant is considered to have completed the study if the Participant completes the Day 365 Visit.

5. STUDY POPULATION

Participants who complete the Day 180 Visit in VMALS-002-2 are eligible to enroll in this extension study, VMALS-002-2b.

5.1. Number of Participants

The number of Participants to be enrolled in this extension study depends upon the number of Participants who complete the Day 180 Visit in VMALS-002-2 and provide written informed consent for this extension protocol (prior to, during, or after their Day 180 Visit in the VMALS-002-2 study).

5.2. Participant Identification

To maintain confidentiality, the name of the Participant should not be recorded on any study document other than the informed consent form. All Participants who sign the informed consent form will be identified by the same unique identifier/number they were assigned in VMALS-002-2.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

There are no meal or dietary restrictions for this study.

5.3.2. Caffeine, Alcohol, and Tobacco

There are no caffeine, tobacco, or alcohol restrictions for this study.

5.3.3. Supplements

There are no restrictions on herbal medicines or dietary supplements or changes in their use during the study. The use of any supplements during the study will be recorded on the Participant's medical record and the electronic case report form (eCRF) as concomitant medications.

5.3.4. Activity

There are no restrictions on activity. Participants should be advised to continue their normal activity level during the study.

6. STUDY INTERVENTION

There will be no treatment administered during this study.

6.1. Measures to Minimize Bias

6.1.1. Randomization

There will be no randomization of Participants in this VMALS-002-2b extension study; Participants who are entered into this extension study will continue to be followed in a blinded fashion.

6.1.2. Blinding

Participants, Investigators, Site staff, CRO staff, and Sponsor staff will remain blinded to treatment assignments except for the designated unblinded Clinical Research Associate (CRA) and the unblinded Medical Monitor.

To avoid potential bias, Investigators and study staff are expected to refrain from sharing safety and treatment outcomes with other participating Sites.

The DSMB, independent of the Sponsor, may review individual unblinded Participant narratives in the case of an SAE or multiple SAEs for which the DSMB Chair requests unblinding, but will not have access to unblinded tables and listings unless requested by the DSMB Chair when assessing a potential safety signal. While the study is ongoing and prior to database lock, the datasets will remain blinded with no preliminary summary of the study by the individual treatment arms except when requested by the DSMB Chair.

6.1.3. Maintenance of the Blind

The treatment assignment for each Participant that was determined by the randomization module in the VMALS-002-2 study will be continued for each Participant in the VMALS-002-2b extension study.

IN CASE OF EMERGENCY (i.e., SERIOUS ADVERSE EVENT [SAE]) AND ONLY WHEN THIS INFORMATION INFLUENCES THE PARTICIPANT'S MEDICAL MANAGEMENT, the Investigator may contact the designated unblinded Medical Monitor to request unblinding of the treatment assignment. The date and reason for unblinding will be documented in the electronic data capture (EDC) system.

6.2. Concomitant Therapy

Standard of care for ALS is presented in the American Academy of Neurology (AAN) guideline regarding management and care of the patient with ALS.[63] Recommendations are presented for multidisciplinary care, symptom management, and the treatment of cognitive/ behavioral impairment.

6.3. Prior and Concomitant Medications, Treatments, and Procedures

Concomitant medications and procedures during VMALS-002-2b from Day 180 of VMALS-002-2 to Day 365 of this extension study will be recorded on the Medication and

History eCRF on the Days 240, 300, and 365/ET. Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, herbal supplements, and procedures that the Participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medications or Concomitant Procedures eCRF. For each medication or treatment, the following information will be collected:

- Medication trade or generic name, or procedure name
- Indication for which the medication/procedure was given
- Dose/strength, route, and frequency of administration of medications
- Date started and date stopped (or continuation at study exit)
- Reason for use of concomitant medications or procedures

The medical monitor must be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1. Participant Withdrawal/Discontinuation

Any Participant may voluntarily discontinue the study at any time without prejudice. The Investigator may discontinue a Participant from the study at any time if, in the Investigator's judgment, the Participant's health or safety would be compromised by remaining in the study.

Specific reasons for study discontinuation include the following:

- Participant decision
- Investigator's decision
- TEAEs or TESAEs
- Insufficient compliance with study requirements
- Lost to follow-up
- Other

The specific reasons for Participant discontinuation will be recorded in the eCRFs.

The following assessments will be performed at an Early Termination (ET) Visit, if possible, for Participants who discontinue prior to the Day 365 Visit.

- Complete Physical examination
- Vital signs, weight, height
- 12-lead ECG
- Serum chemistry and hematology
- Concomitant medications and procedures
- ALSFRS-R
- SVC
- HHD
- ALSAQ-40
- PGIC
- CGIC
- TEAEs, TESAEs, and AESIs

7.2. Lost to Follow-up

A Participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled Visits and is unable to be contacted by the Site between the Day 180 of VMALS-002-2 and the Day 365 (+7 days) of VMALS-002-2b.

The following actions must be taken and recorded if a Participant fails to return to the clinic for a required study Visit:

- The site must attempt to contact the Participant and reschedule the missed Visit as soon as possible. The site must counsel the Participant on the importance of

maintaining the assigned Visit schedule and ascertain whether or not the Participant wishes to and/or should continue in the study.

- If no response is obtained from the Participant, the Investigator is encouraged to contact one of the Participant's relatives or his/her general practitioner.
- Before a Participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the Participant, including at least three telephone calls and, finally, a certified letter to the Participant's last known mailing address. These contact attempts should be documented in the source records.
- Should the Participant continue to be unreachable, the Participant will be considered lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

All study procedures and assessments together with their timing are summarized in the SoA in Section 1.3.

Protocol waivers or exemptions are not allowed. Adherence to the protocol requirements is essential.

8.1. Safety Assessments

The safety assessments listed in Section 1.3 should be followed during the 180-day extension study.

8.1.1. Complete Physical Examinations

A complete physical examination (PE) will be performed on Days 240 and 365/ET. The complete PE will include the following: an examination of the skin/integumentary systems, general appearance, head, neck (including thyroid), eyes, ears, nose, throat, lymph nodes, chest (lungs), heart, abdomen, musculoskeletal system, neurological system, and any additional assessments needed to establish Baseline status or evaluate symptoms or TEAEs. Any abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and clinically significant abnormalities should be recorded as TEAEs, TESAEs, or AESIs. Investigator or qualified medical personnel who routinely perform these evaluations in patients with ALS will conduct the examination, determine findings, and assess any abnormalities as to their clinical significance.

8.1.2. 12-Lead Electrocardiograms

12-Lead ECGs will be performed on Days 240 and 365/ET. Any clinically significant abnormalities are to be recorded as TEAEs. The ECG recording will be printed out and stored with the Participant's records.

8.1.3. Vital Signs

Vital signs will be measured on Days 240, 300, and 365/ET. After resting in the seated position for 5 minutes, vital signs will be recorded including temperature, sitting blood pressure, heart rate, respiratory rate, and oxygen saturation on room air. The method of temperature measurement should be according to the Site's policy and should be consistently applied.

8.1.4. Clinical Laboratory Assessments

The Investigator must review the Participant's laboratory test results reports, document this review, and record any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Participant's condition. Clinically significant abnormal laboratory findings should be recorded as TEAEs, TESAEs, or AESIs using an appropriate medical diagnosis.

Blood sample for laboratory assessments will be collected on Days 240 and 365/ET.

All protocol-required laboratory assessments must be performed in accordance with the laboratory manual and the SoA. The laboratory reports must be filed with the source documents.

8.1.4.1.1. Hematology

- White blood cell count
- Neutrophil count (including calculated absolute neutrophil count)
- Hemoglobin
- Hematocrit
- Platelet count

8.1.4.1.2. Kidney Function Tests

- Blood urea nitrogen (BUN)
- Creatinine

8.1.4.1.3. Liver Function Tests

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase (GGT)
- Total bilirubin
- Total protein
- Albumin

8.1.4.1.4. Clinical Chemistry

- Electrolytes (sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate, magnesium)
- Glucose (random collection, i.e., not necessarily fasting)
- Amylase
- Lipase
- Lactate dehydrogenase
- Creatine kinase

8.1.5. Slow Vital Capacity

Slow vital capacity is a pulmonary function test that quantifies the volume of air that can be slowly exhaled after slow maximum inhalation. SVC will be measured and recorded on

Days 240, 300, and 365/ET. Clinically significant abnormal SVC findings should be recorded as TEAEs, TESAEs, or AESIs.

8.2. Other Assessments and Procedures

8.2.1. Revised Amyotrophic Lateral Sclerosis Functional Rating

The ALSFRS-R is a validated rating scale for measuring the global function of patients with ALS. It provides a health professional-generated estimate of the patient's degree of functional impairment, which can be evaluated serially to objectively assess any response to treatment or progression of disease. The ALSFRS-R includes twelve questions that ask the Investigator to rate his/her impression of the patient's level of functional impairment in performing one of twelve common tasks, e.g., climbing stairs. Each task is rated on a five-point scale from 0 (can't do) to 4 (normal ability). Individual item scores are summed to produce a reported score between 0=worst and 48=best. The ALSFRS-R will be conducted on Days 240, 300, and 365/ET. Details about the scale can be found in Section 10.4, Appendix 4.

8.2.2. Handheld Dynamometry

Muscle strength will be measured quantitatively by HHD and the change from baseline (Day 0, VMALS-002-2) in HHD following Engensis injections as compared to Placebo. HHD is a procedure by which a dynamometer is applied to the body of an individual being tested.[64]

A non-AC powered dynamometer (manufactured by Hoggan Health Industries, Inc) will be used at all clinical sites. These measurements will be performed on Days 240, 300, and 365/ET. Strength measurements will be evaluated for individual muscles.[65]

8.2.3. Quality of Life Assessment, Patient Reported Outcomes, and Clinical Reported Outcomes

8.2.3.1. Amyotrophic Lateral Sclerosis Assessment Questionnaire

The ALSAQ-40 is a disease-specific, Participant self-report health status, or electronic patient-reported outcome (ePRO). There are 40 questions in the ALSAQ-40 with 5 discrete scales: physical mobility (10 questions), activities of daily living and independence (10 questions), eating and drinking (3 questions), communication (7 questions), and emotional reactions (10 questions). The ALSAQ-40 will be measured on Days 240 and 365/ET. See Section 10.5, Appendix 5, for the ALSAQ-40 questionnaire.

Participants are asked to think about the difficulties that they may have experienced during the last two weeks (e.g., "I have found it difficult to feed myself"). Participants are asked to indicate the frequency of each event by selecting one of 5 options (Likert scale): never, rarely, sometimes, often, always, or cannot do at all.

8.2.3.2. Patient Global Impression of Change

The Participant's impression of change at Days 240 and 365/ET will be measured with the PGIC questionnaire through use of the ePRO. This questionnaire measures the Participant's perception

of their level of activity, symptoms, emotions, and overall quality of life during the study. Each descriptor is ranked on a 10-point scale, where Much Worse = 0, No Change = 5, and Much Better = 10. The PGIC questionnaire is presented in Section 10.6, Appendix 6.

Upon completion of the questionnaire by the Participant, the study coordinator will check the questionnaire for completeness. Any omissions or ambiguous answers will be clarified by the Participant prior to leaving the clinic.

8.2.3.3. Clinical Global Impression of Change

The CGIC is a validated instrument completed by observers as an assessment of QoL. The CGIC is a 8-point scale with scores that range from 0 (not conducted) to 1 (very much improved) to 7 (very much worse). The test will be administered during the Days 240 and 365/ET Visits. The CGIC questionnaire is presented in Section 10.6, Appendix 6.

8.3. Treatment-emergent Adverse Events and Treatment-emergent Serious Adverse Events

The definitions of TEAEs and TESAEs can be found in Section 10.2, Appendix 2.

8.3.1. Time Period and Frequency for Collecting TEAE and TESAE Information

All TEAEs and TESAEs will be collected after signing informed consent prior to, on, or after Day 180 of the Study VMALS-002-2 until the time that the Participant completes or withdraws consent for VMALS-002-2b (see definition of TEAE, Section 10.2).

All TESAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2.5, Appendix 2. The Investigator will submit any updated TESAE data to the Sponsor within 24 hours of its availability.

Investigators are not obligated to actively seek TEAEs or TESAEs after conclusion of the study participation. However, if the Investigator learns of any TESAE, including a death, at any time after a Participant has been discontinued from the study, and he/she considers the event to be possibly, probably, or definitely related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting TEAEs and TESAEs

The method of recording, evaluating, and assessing causality of TEAEs and TESAEs, and the procedures for completing and transmitting SAE reports are provided in Section 10.2, Appendix 2.

Care will be taken not to introduce bias when detecting TEAEs and/or TESAEs. Open-ended and non-leading verbal questioning of the Participant is the preferred method to inquire about TEAE occurrences.

8.3.3. SAE Reporting to the Sponsor or Designee

All SAEs should be reported to the Sponsor or designee within 24 hours of knowledge of the SAE occurring (see Section 10.2, Appendix 2).

8.3.4. Adverse Events of Special Interest

Any of the AESIs that occur during the study, as described below, must be recorded as AESI and any of the AESI that meet the criteria for a serious event (Section 8.3) must be reported as a TESAE and identified as an AESI.

Categories of AESIs

There are two main categories of AESIs as presented below: 1) those considered to be related to the angiogenesis potential of Engensis, 2) other medical problems in this patient population, and 3) COVID-19 infections occurring in Participants during the study.

8.3.4.1. AESI Considered Related to Angiogenesis

Atherosclerosis

Hyperplasia of the vasa vasorum in the early stages of atherosclerosis is independent of angiogenesis, but the intimal neovascularization that follows the hyperplasia of the vasa vasorum is angiogenesis-dependent.[66] Angiogenesis increases oxygen and nutrients to the artery wall and supports initial plaque growth. Once the atherosclerotic plaque develops, intimal angiogenesis is thought to contribute to characteristics of an unstable plaque, plaque hemorrhage, and plaque rupture. Therefore, diagnoses suggestive of recent coronary artery disease since Baseline will be evaluated as AESIs.

Cancer

Angiogenesis plays an important role in the proliferation and metastatic spread of cancer as these processes are dependent on an adequate supply of oxygen and nutrients and removal of waste products.[67] All types of cancer reported during the study will be deemed to be AESIs.

8.3.4.2. Other Medical Problems in ALS Patients

Several medical problems are frequently observed in patients with ALS that should be considered AESIs. These medical problems are listed below.

- Pulmonary Medical Problems: Because patients with ALS are at an increased risk to develop pulmonary medial problems such as aspiration of food or liquids. pneumonia, and respiratory arrest, all events of this type that occur during the study will be considered AESIs.

- Progressive Muscle Weakness: Because some patients with ALS may develop rapidly progressive muscle weakness that results in loss of ability to care for self, decubitus ulcers, or weight loss due to impaired deglutition; all events of this type that occur during the study will be considered AESIs.

- Bulbar Disease: Participants may develop bulbar disease or worsening on bulbar disease during the study, manifested as challenges with dysarthria, facial weakness, impaired tongue pulsion or palate elevation, and impaired mastication and swallowing; all of these types of events that occur during the study will be considered AESIs.

8.3.4.3. COVID-19 Infections

A diagnosis of a Corona Virus Disease 2019 (COVID-19) infection occurring in Participants will be recorded as an AESI and their disposition during the trial following the diagnosis of the COVID-19 infection will be tracked.

8.3.5. Follow-up of TEAEs, TESAEs, and AESIs

After the initial TEAE or TESAE report, the Investigator is required to proactively follow each Participant at subsequent Visits/contacts. All TEAEs, TESAEs, and AESIs (see Section 8.3.4) will be followed until resolution, stabilization, the event is otherwise explained, or the Participant is lost to follow-up (as defined in Section 10.2.3, Appendix 2).

8.3.6. Regulatory Reporting Requirements for TESAEs

Prompt notification by the Investigator to Helixmith of an SAE is essential to ensure that legal obligations and ethical responsibilities towards the safety of Participants and the safety of a study drug under clinical investigation are met.

Helixmith has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), and Investigators.

For all studies, Investigator Safety Reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Helixmith's policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator Safety Report describing a TESAE or other specific safety information (e.g., summary or listing of TESAEs) from the Sponsor will review and then notify the IRB if appropriate according to local requirements.

8.3.7. Helixmith's Responsibility

All TEAEs and TESAEs will be reported on an annual basis to FDA in accordance with the IND regulation (21 Code of Federal Regulations [CFR] 312). Per the 2010 FDA Guidance Document for Industry and Investigators "Safety Reporting Requirements for INDs and bioavailability (BA)/bioequivalence (BE) Studies," events categorized as "possibly" or "probably" related will

be treated as "suspected adverse reactions." Events categorized as "definitely" related will be treated as an "adverse reaction" (adverse drug reaction, ADR).

All serious and unexpected study-drug-related adverse reactions (SUSARs) or suspected adverse drug reactions (SADRs) will be reported to FDA and to all participating Investigators in an IND Safety Report within 15 calendar days of the event after Helixmith determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32). Any unexpected fatal or life-threatening study-drug-related adverse reaction or suspected adverse reaction will be reported to the Agency within 7 calendar days after the Sponsor's initial receipt of the information.

Helixmith will notify all participating Investigators of any new safety information that alters the current risk-benefit assessment of the study medication or that would be sufficient to consider changes in Engensis administration or in the overall conduct of the study.

8.3.8. Pregnancy and Contraception

8.3.8.1. Pregnancy Test (Women of Childbearing Potential Only) and Contraception

Female Participants must be nonpregnant, nonlactating, and either postmenopausal for at least 1 year, or surgically sterile for at least 3 months, or agree to use double-barrier contraception from 14 days prior to Day 180 visit in VMALS-002-2 and/or their last confirmed menstrual period prior to Day 180 (whichever is longer) until 2 months after the last visit on Day 365/ET. Double-barrier contraception may include, but is not limited to, intrauterine device with spermicide, female condom with spermicide, diaphragm with spermicide, cervical cap with spermicide; having a male sexual partner who agrees to use a male condom with spermicide; or having a sterile sexual partner.

For women of childbearing potential, a urine beta human chorionic gonadotropin (β-HCG) test will be performed on Day 365/ET to evaluate whether the Participant is pregnant.

The rhythm method, abstinence, outercourse, or celibacy are not considered acceptable method of contraception.

8.3.8.2. Pregnancy

The Investigator will collect pregnancy information on any female Participant who becomes pregnant while participating in this study. The initial information will be submitted to the Helixmith within 24 hours of learning of a Participant's pregnancy.

Further dosing will be discontinued for any female Participant who becomes pregnant during the study.

The Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the Participant and the neonate, and the information will be forwarded to Helixmith. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

While pregnancy itself is not considered to be a TEAE or TESAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as a TEAE or TESAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be a TESAE and will be reported as such. Other abnormal pregnancy outcomes (e.g., fetal death, congenital anomalies, ectopic pregnancy) are also considered TESAEs and will be reported.

Any post-study pregnancy-related SAE considered possibly, probably, or definitely related to the study drug by the Investigator will be reported to the Helixmith. While the Investigator is not obligated to actively seek this information in former study Participants, he or she may learn of an SAE through voluntary reporting.

The Investigator will record a narrative description of the course of each pregnancy and its outcome.

8.3.9. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Except for signs and symptoms of ALS, all disease-related events or disease-related outcomes qualify as TEAEs or TESAEs.

9. STATISTICAL CONSIDERATIONS

Detailed statistical methods are described in the Statistical Analysis Plan (SAP).

9.1. Sample Size Determination

The number of Participants in this study will be determined by the number who complete the Day 180 Visit in VMALS-002-2.

9.2. Population for Analysis: Safety Population

The safety analysis population will contain all Participants who enroll in VMALS-002-2b.

9.3. Statistical Analyses

The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned endpoints.

9.3.1. Primary Endpoints

Safety analyses in this study will evaluate the safety profile of Engensis. The primary endpoints for safety are as follows:

- Incidence of TEAEs, TESAEs, and AESIs
- Incidence of clinically significant laboratory values

No formal statistical testing will be conducted for the safety analyses. All Participants in the Safety Population will be included in these analyses. For data analysis, Participants will be grouped by the treatment received during VMALS-002-2. All summaries will be derived from and based on available data. No imputation will be performed for missing values. All safety analyses will be made on the Safety Population.

9.4. Data Safety Monitoring Board

The independent DSMB will also perform a Safety Review, using a limited set of unblinded tables and/or listings of all safety data, including all reported AESIs, TEAEs, and TESAEs. The DSMB may perform multiple unblinded analyses for safety during the study.

The objectives of the DSMB meetings are to review the safety outcomes of the study and provide guidance to Helixmith regarding the safety of Engensis. The data analyses for the DSMB meetings will be directly provided to the DSMB members, and no data will be released to the study sponsor or blinded designees. Information will only be shared with Helixmith or the Helixmith Project Steering Committee when the DSMB recommends a temporary suspension or termination of the study. No adjustment will be made for multiple testing due to the DSMB data reviews. Further details of DSMB responsibilities are included in the DSMB Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

10.1.1.1. Institutional Review Board

Prior to the initiation of the study, the protocol, the informed consent form, and Investigator's Brochure will be submitted to the IRB for approval. By signing the "Statement of Investigator" form (Form FDA 1572), the Investigator is ensuring that an IRB compliant with the requirements set forth in 21 CFR 56 will be responsible for the initial and continuing review of the proposed clinical study. A copy of the IRB approval letter for the protocol, the informed consent, and the protocol signature page must be submitted to the Sponsor prior to release of investigational supplies to the Study Site. The approval letter must refer to the specific protocol and the informed consent form. The Study Site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol. A list of the IRB members, their titles or occupations, and their institutional affiliation, or an IRB assurance number must be provided to the Sponsor prior to release of study supplies.

Health authority regulations require that all advertisements for Participant recruitment be approved by an IRB prior to implementation. The complete text and format must be submitted to the Sponsor for approval prior to IRB submission.

The Investigator is responsible for notifying the IRB of any SAEs as required by the IRB. A copy of the notification must be forwarded to the Sponsor or its designee.

Status reports must be submitted to the IRB at least once a year (or more frequently as required by the IRB), and the IRB must be notified of completion or termination of the study.

10.1.1.2. Informed Consent Process

The Investigator has the responsibility to inform each Participant, prior to, on, or after the Day 180 Visit in VMALS-002-2, of the purpose of this clinical study, including possible risks and benefits, and document the informed consent process in the Participant's chart. An informed consent form (ICF) containing the required GCP elements of informed consent must be generated by the Investigator. After approval by the Sponsor, the ICF must be submitted to and approved by an IRB. Prior to entry into the study or initiation of any study-related procedures, the Participant must read, sign, and date the ICF. The person executing the consent must also sign and date the IRB-approved ICF. One original ICF is to be retained by the Study Site, and a copy is to be given to the Participant. The informed consent process must be documented in the Participant's source/medical record.

The ICF must be written in a language in which the Participant is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language ICFs be submitted to the IRB for approval. The Investigator must

forward a copy of the ICF, the certified foreign language translation, and an IRB approval letter to the Sponsor.

The Investigator will explain the study purpose, procedures, and Participant's responsibilities to the Participant. The Participant's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained. The Participant will sign and date the ICF. The Investigator or a qualified designee will also sign and date the ICF. The original ICF will be retained with the Participant's records; a copy will be provided to the Participant.

If the ICF is amended during the study, the Investigator or a qualified designee must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB. For each new version of the ICF, the IRB will be consulted to determine if Participants who have not completed the study must be re-consented to the new ICF.

10.1.1.3. Obligations of the Helixmith and the Investigator

Helixmith and the Investigator must comply with all applicable regulations. In addition, the Investigator must follow local and institutional requirements pertaining, but not limited, to clinical research, informed consent including the use and disclosure of the Participants' protected health information (PHI), and IRB regulations. Helixmith will notify the Investigator of protocol and amendment approvals by regulatory authorities when applicable.

The Investigator and clinical research coordinator will be available to respond to reasonable requests and audit queries made by the authorized regulatory agency representatives. The Investigator and clinical research coordinator will provide Helixmith with advance written notification if they plan to relocate to another institution.

Except where the Investigator's signature is specifically required, the term "Investigator" as used in this protocol and protocol-related documents is understood to refer to the Principal Investigator (PI) or appropriate Study Site personnel whom the PI designates to perform a certain duty. This delegation of authority needs to be documented appropriately and signed by the PI. The PI is ultimately responsible for the conduct of all aspects of the clinical study.

Sub-investigators or other appropriate Study Site personnel (e.g., listed on the Form FDA 1572) are eligible to sign for the PI on laboratory reports and may be designated to verify and electronically sign eCRFs.

10.1.2. Financial Disclosure

10.1.2.1. Conflict of Interest Policy

The independence of the study from any actual or perceived influence is critical. Therefore, any actual conflict of interest or financial interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study should be disclosed. Furthermore, persons who have a perceived conflict of interest or financial interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study.

10.1.2.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Participant Selection and Informed Consent Process

Participants who completed the Day 180 visit in VMALS-002-2 and are planned for enrollment in VMALS-002-2b, must sign an ICF that has been approved both by Helixmith and reviewed by the Independent Ethics Committee (IEC)/IRB. The informed consent should be in accordance with the current revision of the Declaration of Helsinki as well as current ICH and GCP guidelines.

On Day 180 of the VMALS-002-2 study, Participants will receive a comprehensive explanation of the VMALS-002-2b study including the nature and risks of the study, alternate therapies, any known AEs, and the other elements that are part of obtaining proper informed consent. Potential Participants will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically any saved blood samples. Potential Participants will be allowed sufficient time to consider participation in the study after having the nature and risks of the study explained to them. The ICF must not include any exculpatory statements. The ICF and any separate Health Insurance Portability and Accountability Act (HIPAA) authorization form, if applicable, should be reviewed and approved by the Helixmith prior to IRB/IEC submission.

Helixmith will provide to the Investigator, in writing, any new information that significantly bears on the Participants' risk in receiving the study drug. This new information will be communicated by the Investigator to Participants in accordance with IRB/IEC requirements. The ICF will be updated, and Participants will be re-consented.

Site staff may conduct standard-of-care procedures and employ recruitment efforts prior to Participant consent; however, before any protocol-specified procedures are performed to determine protocol eligibility, an ICF must be signed. Participants will be given a copy of all consent forms that they sign.

By signing the ICF, the Participant agrees to complete all evaluations required by the study unless the Participant withdraws voluntarily or is terminated from the study for any reason.

10.1.4. Data Protection and Confidentiality

The data resulting from this study will be the proprietary information of Helixmith and may be made public after all data have been analyzed and the study results are available. At the end of the study, a clinical study report will be written by Helixmith.

10.1.4.1. Confidentiality

Participant confidentiality and privacy are strictly held in trust by the Investigators, their staff, and Helixmith. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to Participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of Helixmith.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of Helixmith, representatives of the IRB, regulatory agencies, or pharmaceutical companies supplying study product may inspect all documents and records required to be maintained by the Investigator including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for Participants. The Clinical Study Site will permit access to such records.

The Participant's contact information will be securely stored at each Clinical Site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, applicable regulatory agencies, institutional policies, and/or Helixmith requirements.

Participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor or their designee. This will not include the Participant's contact or identifying information. Rather, individual Participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by Clinical Sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.1.4.2. Data Protection

In accordance with GCP and with the international/national data protection laws, all information concerning the Participants in the study must be treated as strictly confidential by all persons involved in the study.

The Investigator acknowledges that any and all information acquired from Helixmith or developed or acquired in connection with the study is strictly confidential. The Investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of Helixmith in writing. Such consent will be deemed to have been given for disclosure to any person for whom the Investigator is responsible at his/her center, but only so far as required for the purposes of the study. In the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

Potential Participants must be informed that their personal study-related data will be used by Helixmith in accordance with GCP, international/national, and local data protection law. The

level of disclosure must also be explained to the Participant who will be required to give consent for their data to be used as described in the ICF.

Potential Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Helixmith, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Committee Structure

10.1.5.1. Data Safety Monitoring Board

An independent DSMB has been chartered for this study to review all safety data during the study and safeguard the interests of the Participants. The objectives of the DSMB meetings are to review the safety outcomes of the study and provide guidance to the Sponsor regarding the safety of Engensis. The DSMB will meet periodically and review a limited set of unblinded or noncomparative tables and/or listings of all reported TEAEs, TESAEs, and AESIs. If a safety signal is identified during the noncomparative analysis, this will be followed by a comparative analysis as prompted by observations. The data analyses for the DSMB meetings will be directly provided to the DSMB members; no data will be released to the Sponsor or blinded designees. No adjustment will be made for multiple testing due to the DSMB data review.

The DSMB will consist of two physicians with expertise in clinical studies and one statistician. Members of the DSMB will be independent of study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflicts of interest. An independent biostatistician will be available for consultation.

The DSMB will operate under the rules of the charter, which have been reviewed at organizational meetings of the DSMB. Routine DSMB meetings will be regularly scheduled per the DSMB Chair to review safety and pooled all-cause mortality data, including unblinded Participant narratives. The DSMB Chair may request additional unblinded information at any time to further understand a safety trend. Ad hoc DSMB meetings can be convened at any time at the discretion of the DSMB Chair or the Sponsor. However, the DSMB Chair may not share any unblinded information with the Sponsor unless it is deemed necessary for the Sponsor to address a potential safety concern. The DSMB will provide recommendations to the Sponsor in accordance with the DSMB Charter.

10.1.6. Data Quality Assurance

10.1.6.1. Clinical Monitoring

Helixmith or designee will visit (in person or remotely, according to FDA Guidance on Conduct of Clinical Trials of Medical Product during COVID-19 Pandemic, March 2020, updated 03 Jun 2020) the Clinical Site for monitoring. The Helixmith's clinical monitor shall ensure that the Investigator understands the investigational status of the product, all protocol requirements, and his/her regulatory responsibilities as an Investigator. The clinical monitors will visit (in person or remotely) Clinical Sites at appropriate intervals to ensure compliance with the protocol and to

verify the accuracy, completeness, and correctness of data reported and accountability of Engensis supplies.

The clinical monitor shall be available for consultation by the Investigator and serves as a liaison between the Clinical Site and Helixmith. The clinical monitor or other authorized representatives of Helixmith may inspect all data, documents, and records required to be maintained by the Investigator including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for Participants. The Clinical Site will permit access to such records. The Investigator will obtain, as part of the informed consent process, HIPAA-compliant authorization from Participants to use and disclose the requisite and relevant PHI and permission for authorized representatives of Helixmith, or regulatory authorities including the FDA, to review, in confidence, any records identifying Participants in the clinical study.

10.1.6.2. Access to Study Documents and Study Monitoring

Helixmith has designated a Contract Research Organization (CRO) to monitor the progress of this study. The CRO clinical monitor, as a representative of Helixmith, has the obligation to follow this study closely. Helixmith or its designee may meet with Investigators prior to the initiation of the study in order to review the adequacy of the Participant population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator with the study protocol.

Helixmith or its designee may meet with the Investigator(s) at the time that study Participants begin to be enrolled to ensure that Participants are being properly selected and that study data are being correctly recorded.

During the study, the clinical monitor will visit (in person or remotely) the study facilities regularly and use telephone and written communications on an ongoing basis to maintain current knowledge of the study. During periodic visits to the Clinical Site (in person or remotely), the monitor will review the source documents used for data entry in the EDC system to verify the accuracy and completeness of the information contained in those reports in preparation for retrieval. Source documents must contain all data entered in the EDC system. All data generated during this study and the source documents from which they originated are subject to inspection by Helixmith or its representatives, and the FDA and other regulatory agencies.

Upon completion of the study, the clinical monitor will conduct a final visit (closeout) to the Site. The objectives of this visit are to ascertain that all regulatory records are complete, verify that study drug and other supplies have been accounted for, and ensure that the Investigator is aware of his/her responsibilities post-study.

10.1.6.3. Quality Assurance and Quality Control

Each Clinical Site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality Control (QC) procedures will be conducted within the EDC. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Following written Standard Operating Procedures (SOPs) by the CRO, the monitors will verify that the clinical study is conducted, data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices [GLP]).

The Clinical Site will provide direct access to all study-related source data documents and reports for the purpose of monitoring and auditing by Helixmith, and inspection by local and regulatory authorities.

The study will be conducted in accordance with the principles of GCPs: 21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 312, Subpart D; the 2016 ICH Guideline on Good Clinical Practice (ICH E6(R2)); and HIPAA.

The Investigator at a Clinical Site must sign the Investigator Statement of Agreement.

10.1.6.4. Data Quality Assurance

Helixmith's employees and/or their contracted representatives use SOPs designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and GCP guidance.

A quality assurance audit may be conducted by Helixmith or its designee at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to, a review of all ICFs, source documents, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the noted observations.

All Participant data relating to the study will be recorded on eCRFs unless transmitted to the Helixmith or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that eCRF data entries are accurate, correct, and complete by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

Helixmith is responsible for the data management of this study including quality checking of the eCRF data.

Helixmith assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized Site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of Participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.6.5. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff under the supervision of the Investigator. During the study, the Investigator will maintain complete and accurate documentation for the study. The Investigator should ensure that the Participant is provided with instructions and is trained to use the ePRO and to complete the assessment tool properly before data collection begins.

All eCRF data will be entered into a validated database compliant with 21 CFR Part 11. Laboratory data will be either manually entered or imported to the clinical database electronically. All data entry, verification, and validation will be performed in accordance with the current SOPs of Helixmith or its designee. The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures are completed.

The Clinical Site will be provided with eCRFs in which to record all the protocol-specified data for each Participant. Entries made in the eCRF must be verifiable against source documents, or in certain circumstances as directed by the Helixmith, entries will have been directly entered into the eCRF; in such cases, the entry in the eCRF will be considered as the source data. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. The Investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each Participant's eCRF, verifying that the information is true and correct. Queries generated by Data Management will be sent to the Clinical Site for resolution. The Investigator is responsible for the review and approval of all responses to eCRF queries.

10.1.6.6. Protocol Deviations

The Investigator will not deviate from this protocol for any reason without prior written approval by the Medical Monitor on behalf of the Helixmith except in the case of a medical emergency when the change is necessary to eliminate an apparent and immediate hazard to the Participant. Protocol deviations are to be recorded in source documents and will be tracked through the EDC.

In the event of such an emergency, the Investigator will notify the Medical Monitor immediately by phone, notify the IRB, and confirm with the Medical Monitor in writing within 5 working days of the change being implemented.

10.1.6.7. Source Documents

As defined in the ICH Guidelines for Good Clinical Practice E6(R2), Section 1.52, source documents may include: original documents, data, and records (e.g., hospital records, clinical

and office charts, laboratory notes, memoranda, Participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x rays, Participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).

Source documents provide evidence for the existence of the Participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's Site.

The Investigator may need to request previous medical records or transfer records. Current medical records must also be available.

10.1.7. Data Management

All Participant data will be entered into a password-protected validated EDC system by authorized Site personnel according to the CRO's SOPs.

Data discrepancies identified via programmed edit checks, manual data review or discovered during data monitoring will be addressed and resolved. An audit trail in the EDC system will list all changes made to the data, with a date/time stamp and user initials. Upon database lock, occurring after data are declared clean and eCRFs have been approved by the Investigator, the CRO will provide SAS datasets to the Sponsor and designated Statistician for data analysis via secure data transfer specified in the Study Data Management Plan.

10.1.8. Recordkeeping and Retention

Data generated for the study should be stored in a limited-access and secured-access file area and be accessible only to representatives of the Clinical Site, Helixmith and its representatives, and FDA/relevant health authorities/regulatory agencies. All reports and communications relating to Participants will identify Participants only by Participant identification number. Complete Participant identification will be kept by the Investigator. This information will be treated with strict adherence to professional standards of confidentiality and personal data protection laws.

The Investigator must in reasonable time, upon request from any properly authorized officer or employee of FDA/relevant health authority/regulatory agency, permit such officer or employee to have access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by the FDA/relevant health authority/regulatory agency, the Investigator will contact Helixmith immediately. The Investigator will also grant Helixmith's representatives the same privileges offered to FDA/relevant health authority or regulatory agents/officers/employees.

The Investigator must provide Helixmith or its designee with the following documents prior to study initiation and retain a copy in the study file:

- A completed and signed Form FDA 1572. If, during the study, any changes occur that are not reflected on the current 1572, a new 1572 must be completed and returned to the Sponsor or its designee for submission to the FDA

- Current signed curricula vitae (within 2 years prior to study initiation) and current medical licenses for the Investigator and all co-Investigators listed on the 1572
- A copy of the original approval by the IRB for conducting the study. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy
- A copy of the IRB-approved ICF
- The IRB member list and/or US Department of Human Health Services (DHHS) General Assurance Number (if the IRB has an Assurance number)
- A copy of the original approval by the Institutional Biosafety Committee (IBC) for conducting the study, if applicable. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IBC policy
- Signed Financial Disclosure Forms for all personnel listed on the 1572 with a statement of non-voting by study staff
- The signature page of this protocol signed and dated by the Investigator
- The signature page of the IB signed and dated by the Investigator
- In addition to the documents listed above, the Clinical Site will also retain the following items:
    - Certifications and laboratory reference ranges for all local laboratories used for this study
    - A copy of delegation of authority log
    - Copies of the initiation visit report, the protocol, IB, enrolment logs, subject identifier (ID) list (not provided to sponsor/CRO), investigational product accountability records
    - All original ICFs with required signatures
    - All IRB correspondence (e.g., informed consent [including any approved revisions], protocol, TEAE, advertisements, newsletters)
    - A copy of the Study Monitoring Log
    - Clinical and nonclinical supply shipment forms
    - Copies of all pertinent correspondence pertaining to the study (except budget issues) between the Sponsor, CRO, and the Site
    - Copies of all SAE reports submitted to the Sponsor
    - Copies of all Investigator Safety Reports submitted to the Site by the Sponsor
    - Copies of approved package labelling, if applicable

10.1.9. Study and Site Start and Closure

The study may be suspended temporarily or terminated prematurely by Helixmith for any safety, ethical, or administration reason at any time. Written notification documenting the reason for

study suspension or termination will be provided by the Helixmith to Investigators and regulatory authorities. If the study is prematurely terminated or suspended, the Investigator will promptly inform Participants and the IRB and will provide the reasons for the termination or suspension. Participants will be contacted, as applicable, and be informed of changes to Study Visit schedules.

Helixmith or designee reserves the right to close a Clinical Site or terminate the study at any time for any reason at the sole discretion of Helixmith. Study sites will be closed upon study completion.

The Investigator may initiate Clinical Site closure at any time, provided reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a Clinical Site by Helixmith or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Helixmith's procedures, or GCP guidelines
- Inadequate recruitment of Participants by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, Helixmith will promptly inform the Investigators, IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the Participants and should ensure appropriate Participant therapy and/or follow-up.

10.1.10. Publication Policy

The study will be conducted in accordance with the publication and data sharing policies and regulations as defined in the agreement between Helixmith and the institution. In addition, this study will be registered at www.ClinicalTrials.gov and in any other protocol registries required by the regions in which the study is conducted, and the results from this study will become publicly available.

None of the data resulting from this study will be allowed to be presented or published in any form by the Investigator or any other person without the prior written approval of the Sponsor.

10.1.11. Insurance

Matters relating to insurance for this study are to be defined in the agreement between the Helixmith and the institution.

10.2. Appendix 2. Treatment-Emergent Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of TEAEs

TEAE Definition
• A TEAE is any untoward medical occurrence associated with the use of an investigational product or study procedure in a clinical study Participant, whether or not considered related to the study intervention. • NOTE: A TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention or procedure. • An event that emerges during treatment, having been absent at pretreatment, or worsens relative to the pretreatment state, as defined in the E9 Guidance. • The TEAE is not related to causality / drug relatedness. It may or may not be related to the drug but is considered a TEAE due to its appearance at or after the treatment has been administered.

Events Meeting the TEAE Definition
• Any abnormal laboratory test results (hematology, or clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an TEAE/TESAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the TEAE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the Participant's

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the TEAE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Criteria for Defining a TESAE

If an event is not a TEAE per the definition above, then it cannot be an TESAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An TESAE is defined as any untoward medical occurrence that at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the Participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the Participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the TEAE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an SAE.
d. Results in persistent disability/incapacity • The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the Participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.2.3. Definition of TESAE

Treatment-Emergent Serious Adverse Event is defined as:

- A serious event that emerges during treatment, having been absent at pretreatment, or worsens relative to the pretreatment state, as defined in the E9 Guidance.
- The TESAE is not related to causality / drug relatedness. It may or may not be related to the drug but is considered a TESAE due to its appearance at or after the treatment has been administered.

10.2.4. Recording and Follow-Up of TEAEs and TESAEs

TEAE and TESAE Recording

- When a TEAE or TESAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant TEAE or TESAE information in the TEAE/TESAE eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the Participant's medical records to the Sponsor or designee in lieu of completion of the TEAE/TESAE eCRF page.
- Instances may arise when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all Participant identifiers, with the exception of the Participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the TEAE/TESAE.

Assessment of Intensity

The Investigator will assess the intensity of each TEAE and TESAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. A TEAE that is assessed as severe should not be confused with an TESAE. Severe is a category used for rating the intensity of an event; and both TEAEs and TESAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of a TESAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each TEAE/TESAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each TEAE/TESAE, the Investigator **must** document in the medical notes that he/she has reviewed the TEAE/TESAE and has provided an assessment of causality.
- Situations may arise in which a TESAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, the Investigator must always assess causality for every event before the initial transmission of the TESAE data to the Sponsor or designee. Death or hospitalization are not to be specified as a TESAE; these are criteria to determine seriousness.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an TESAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of TEAEs and TESAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the TEAE or TESAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated TESAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.2.5. Reporting of TESAEs

TESAE Reporting to the Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an TESAE to the Sponsor or designee will be the eCRF. • The Site will enter the TESAE data into the electronic system as soon as it becomes available. • After the study is completed at a given Site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a Site receives a report of a new TESAE from a study Participant or receives updated data on a previously reported TESAE after the electronic data collection tool has been taken off-line, then the Site can report this information to the Medical Monitor or TESAE coordinator by telephone.

10.3. Appendix 3. List of Abbreviations and Definitions

10.3.1. Abbreviations

Abbreviation	Definition
AAN	American Academy of Neurology
AESI	Adverse event of special interest
ALS	amyotrophic lateral sclerosis
ALSAQ	Amyotrophic Lateral Sclerosis Assessment Questionnaire
ALT	alanine transaminase (SGPT)
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
AST	aspartate transaminase (SGOT)
BA	bioavailability
BE	bioequivalence
β-HCG	beta human chorionic gonadotropin
BUN	blood urea nitrogen
cDNA	Complimentary deoxyribose nucleic acid
CFR	Code of Federal Regulation
CLI	critical limb ischemia
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Corona Virus Disease 2019
CGIC	Clinical Global Impression of Change
CNS	central nervous system
CRA	Clinical Research Associate
CRO	contract research organization
CS	clinically significant
DHHS	US Department of Health and Human Services
DNA	deoxyribonucleic acid
DPN	diabetic peripheral neuropathy
DSMB	Data Safety Monitoring Board
EAAT2	excitatory amino acid transporter 2
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
ePRO	electronic patient reported outcome
ET	early termination from the study
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	good clinical practices
GDNF	glial cell line neurotrophic Factor
GGT	gamma-glutamyl transpeptidase

Abbreviation	Definition
GLP	good laboratory practices
HCG	human chorionic gonadotropin
HEENT	head, eyes, ears, nose, and throat
HGF	hepatocyte growth factor
HGF-X7	hybrid hepatic growth factor coding sequence expressing two isoforms of HGF, HGF_{728} and HGF_{723}
HHD	Handheld Dynamometer
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	identifier
IEC	Independent Ethics Committee
IM	intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ISR	Injection site reaction
LLOQ	lower limit of quantitation
MCP-1	monocyte chemoattractant protein 1
MRC	Medical Research Council
NCS	not clinically significant
NGF	nerve growth factor
NDA	New Drug Application
NHU	nonhealing foot ulcers
NMDA	N-methyl-D-aspartate
NO	nitrous oxide
PAD	peripheral arterial disease
PE	physical examination
PGE2	prostaglandin E2
PHI	protected health information
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PRO	patient reported outcome
PTT	partial prothrombin time
QC	quality control
QoL	Quality of Life
RNA	ribonucleic acid
SADR	Suspected adverse drug reaction

Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SoA	Schedule of Activities
SOD1	superoxide dismutase 1
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVC	Slow Vital Capacity
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNF	tumor necrosis factor
US	United States
VEGF	vascular endothelial growth factor

10.3.2. Definitions

Active Infection	Chronic infection or severe active infection that may compromise the Participant's wellbeing or participation in the study, in the Investigator's judgment
Day 240, etc.	Day 240 (for example) refers specifically to the actual day of the Visit designated as the Day 240 Visit, and not to the 240th day of the study for a Participant.
End of Study	Completion of the last Visit (Day 365) or procedures shown in the SoA for the last Participant remaining in the study
Highly Effective Contraception Method	See Contraceptive Guidance
Investigator	The PI or appropriate study site personnel whom the PI designates to perform a certain duty
Safety Analysis Population	All Participants in the study
Sponsor	Helixmith Co., Ltd. and its representatives contracted to provide services for study conduct
Participant	Anyone who is consented for the Safety Evaluation during VMALS-002-2b on or prior to Day 180 of VMALS-002-2
VM202	The active pharmaceutical ingredient of Engensis: a novel genomic complementary deoxyribonucleic acid (cDNA) hybrid human hepatocyte growth factor (HGF) coding sequence (HGF-X7) expressing two isoforms of HGF, HGF_{728} and HGF_{723}

10.4. Appendix 4. Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

Bulbar	Fine Motor	Gross Motor	Breathing

1. Speech
4. Normal speech processes
3. Detectable speech disturbance
2. Intelligible with repeating
1. Speech combined with nonvocal communication
0. Loss of useful speech

2. Salivation
4. Normal
3. Slight but definite excess of saliva in mouth; may have nighttime drooling
2. Moderately excessive saliva; may have minimal drooling
1. Marked excess of saliva with some drooling
0. Marked drooling; requires constant tissue or handkerchief

3. Swallowing
4. Normal eating habits
3. Early eating problems-occasional choking
2. Dietary consistency changes
1. Needs supplemental tube feeding
0. NPO (exclusively parenteral or enteral feeding)

4. Handwriting
4. Normal
3. Slow or sloppy; all words are legible
2. Not all words are legible
1. Able to grip pen but unable to write
0. Unable to grip pen

5a. Cutting Food / Handling Utensils
4. Normal
3. Somewhat slow and clumsy, but no help needed
2. Can cut most foods, although clumsy and slow; some help needed
1. Food must be cut by someone, but can still feed slowly
0. Needs to be fed

5b. Cutting Food / Handling Utensils (Alt. for patients with Gastrostomy)
4. Normal
3. Clumsy but able to perform all manipulations independently
2. Some help needed with closures and fasteners
1. Provides minimal assistance to caregiver
0. Unable to perform any aspect of task

6. Dressing and hygiene
4. Normal function
3. Independent and complete self-care with effort or decreased efficiency
2. Intermittent assistance or substitute methods
1. Needs attendant for self-care
0. Total dependence

7. Turning in bed
4. Normal
3. Somewhat slow and clumsy, but no help needed
2. Can turn alone or adjust sheets, but with great difficulty
1. Can initiate, but not turn or adjust sheets alone
0. Helpless

8. Walking
4. Normal
3. Early ambulation difficulties
2. Walks with assistance
1. Non-ambulatory functional movement only
0. No purposeful leg movement

9. Climbing stairs
4. Normal
3. Slow
2. Mild unsteadiness or fatigue
1. Needs assistance
0. Cannot do

10. Dyspnea
4. None
3. Occurs when walking
2. Occurs with one or more of the following: eating, bathing, dressing (ADL)
1. Occurs at rest, difficulty breathing when either sitting or lying
0. Significant difficulty, considering using mechanical respiratory support

11. Orthopnea
4. None
3. Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows
2. Needs extra pillow in order to sleep (more than two)
1. Can only sleep sitting up
0. Unable to sleep

12. Respiratory insufficiency
4. None
3. Intermittent use of BiPAP
2. Continuous use of BiPAP
1. Continuous use of BiPAP during the night and day
0. Invasive mechanical ventilation by intubation or tracheostomy

10.5. Appendix 5. Amyotrophic Lateral Sclerosis Assessment Questionnaire

The following is an example of the ALSAQ-40

Please complete this questionnaire as soon as possible. If you have any difficulties filling in the questionnaire by yourself, please get someone else to help you with it. However, it is your responses that we are interested in.

The questionnaire consists of a number of statements about difficulties that you may have experienced during the last 2 weeks. There are no right or wrong answers: your first response is likely to be the most accurate for you. Please tick the box which best describes your own experience or feelings.

Please try to answer every question even though some may seem rather similar to others or may not seem relevant to you.

All the information you give will be treated in the strictest confidence.

The following statements all refer to difficulties that you
may have had **during the last 2 weeks**.
Please indicate, by ticking the appropriate box, how often
the following statements have been true for you.

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot walk at all
please tick **Always/cannot walk at all**.

How often during the last 2 weeks have the following been true?

Please tick one box for each question

	Never	Rarely	Sometimes	Often	Always or cannot walk at all
1. I have found it difficult to walk short distances, e.g. around the house.	☐	☐	☐	☐	☐
2. I have fallen over while walking.	☐	☐	☐	☐	☐
3. I have stumbled or tripped while walking.	☐	☐	☐	☐	☐
4. I have lost my balance while walking.	☐	☐	☐	☐	☐
5. I have had to concentrate while walking.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question**
before going to the next set of questions

The following statements all refer to certain difficulties that you may have had <u>during the last 2 weeks</u>. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot do the activities at all
please tick **Always/cannot do at all**.

How often during the last 2 weeks have the following been true?

*Please tick **one box** for each question*

	Never	Rarely	Sometimes	Often	Always or cannot do at all
6. Walking has tired me out.	☐	☐	☐	☐	☐
7. I have had pains in my legs while walking.	☐	☐	☐	☐	☐
8. I have found it difficult to go up and down stairs.	☐	☐	☐	☐	☐
9. I found it difficult to stand up.	☐	☐	☐	☐	☐
10. I have found it difficult to get myself up out of chairs.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question**
before going to the next set of questions

The following statement all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot do the activities at all
please tick **Always/cannot do at all**.

How often during the last 2 weeks have the following been true?

Please tick ***one box*** *for each question*

	Never	Rarely	Sometimes	Often	Always or cannot do at all
11. I have had difficulty using my arms and hands.	☐	☐	☐	☐	☐
12. I have found turning and moving in bed difficult.	☐	☐	☐	☐	☐
13. I have found picking up things difficult.	☐	☐	☐	☐	☐
14. I found holding books and newspapers, or turning pages, difficult.	☐	☐	☐	☐	☐
15. I have difficulty writing clearly.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question**
before going to the next set of questions

The following statement all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot do the activities at all
please tick **Always/cannot do at all**.

How often during the last 2 weeks have the following been true?

Please tick ***one box*** *for each question*

	Never	Rarely	Sometimes	Often	Always or cannot do at all
16. I have found it difficult to do jobs around the house.	☐	☐	☐	☐	☐
17. I have found it difficult to feed myself.	☐	☐	☐	☐	☐
18. I have had difficulty combing my hair or cleaning my teeth.	☐	☐	☐	☐	☐
19. I have had difficulty getting dressed.	☐	☐	☐	☐	☐
20. I have difficulty washing the hand basin.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question**
before going to the next set of questions

The following statement all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot do the activities at all
please tick **Always/cannot do at all**.

How often during the last 2 weeks have the following been true?

Please tick ***one box*** *for each question*

	Never	Rarely	Sometimes	Often	Always or cannot do at all
21. I have had difficulty swallowing.	☐	☐	☐	☐	☐
22. I have had difficulty eating sold foods.	☐	☐	☐	☐	☐
23. I have found it difficult to drink liquids.	☐	☐	☐	☐	☐
24. I have found it difficult to participate in conversations.	☐	☐	☐	☐	☐
25. I have felt that my speech has not been easy to understand.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question**
before going to the next set of questions

The following statement all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot do the activities at all
please tick **Always/cannot do at all**.

How often during the last 2 weeks have the following been true?

Please tick ***one box*** *for each question*

	Never	Rarely	Sometimes	Often	Always or cannot do at all
26. I have slurred or stuttered while speaking.	☐	☐	☐	☐	☐
27. I have had to talk very slowly.	☐	☐	☐	☐	☐
28. I have talked less than I used to do.	☐	☐	☐	☐	☐
29. I have been frustrated by my speech.	☐	☐	☐	☐	☐
30. I have felt self-conscious about my speech.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question**
before going to the next page

The following statement all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true:

*Please tick **one box** for each question*

	Never	Rarely	Sometimes	Often	Always
31. I have felt lonely.	☐	☐	☐	☐	☐
32. I have been bored.	☐	☐	☐	☐	☐
33. I have felt embarrassed in social situations.	☐	☐	☐	☐	☐
34. I have felt hopeless about the future.	☐	☐	☐	☐	☐
35. I have worried that I am a burden to other people.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question** before going to the next set of questions

The following statement all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true:

*Please tick **one box** for each question*

	Never	Rarely	Sometimes	Often	Always
36. I have wondered why I keep going.	☐	☐	☐	☐	☐
37. I have felt angry because of the disease.	☐	☐	☐	☐	☐
38. I have felt depressed.	☐	☐	☐	☐	☐
39. I have worried about how the disease will affect me in the future.	☐	☐	☐	☐	☐
40. I have felt as if I have no freedom.	☐	☐	☐	☐	☐

Please make sure that you have ticked **one box for each question.**

Thank you for completing this questionnaire.

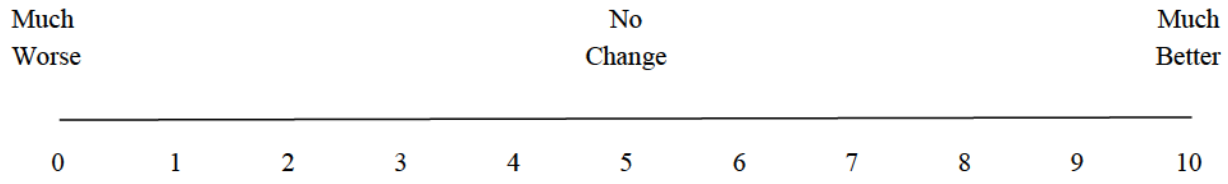
10.6. Appendix 6. Patient Global Impression of Change and Clinical Impression of Change

PGIC Scale:

Since beginning treatment at this clinic, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall quality of life, related to your painful condition? (tick ONE box)

No change (or condition has got worse)	☐	1
Almost the same, hardly any change at all	☐	2
A little better, but no noticeable change	☐	3
Somewhat better, but the change has not made any real difference	☐	4
Moderately better, and a slight but noticeable change	☐	5
Better, and a definite improvement that has made a real and worthwhile difference	☐	6
A great deal better, and a considerable improvement that has made all the difference	☐	7

In a similar way, please circle the number below, that matches your degree of change since beginning care at this clinic:



Clinical Impression of Change Scale

1. CGIC - Global Improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
Compared to his/her condition at admission to the project, how much has he/she changed?

0 = Not assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

2. Efficacy index: Rate this item on the basis of **drug effect only**.
Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Does not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided Improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

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