A PHASE I/II, OPEN LABEL STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF VM202 IN SUBJECTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Protocol VMALS-001 / B

September 15, 2013

Sponsor
ViroMed Co., Ltd.
[redacted]

Worldwide Headquarters:
[redacted]

DISCLOSURE STATEMENT

[redacted]

INVESTIGATOR'S AGREEMENT

I, the undersigned, am responsible for the conduct of the study at the site below and agree to the following:

- I understand that this protocol is a confidential document. I agree that the information within it will not be disclosed to anyone without prior written authority from the sponsor, VM BioPharma, Inc. except to the extent necessary to conduct this study and obtain approval from an ethical review committee or other approving body.
- I understand and will conduct the study according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board, except where necessary to prevent any immediate danger to the subject.
- I have read and understand fully the Investigator Brochure.
- I have sufficient time to properly conduct and complete the study within the agreed study period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.
- I will ensure that any staff members at my site(s) who are involved in the study conduct are adequately trained regarding this trial's operations, the protocol and their responsibilities. In the case of delegating any of my study responsibilities I will provide the sponsor with a delegation of Investigators responsibilities log.
- I understand that the study may be terminated or enrollment may be suspended at any time by VM BioPharma, Inc. with or without cause, or by me or my institution if it becomes necessary to protect the best interest of the study subjects.

Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

PROTOCOL TITLE	A Phase I/II, Open Label, Study to Assess the Safety and Tolerability of VM202 in Subjects with Amyotrophic Lateral Sclerosis
STUDY PHASE	I/II
INVESTIGATIONAL AGENT	VM202
DOSE	64 mg of VM202
POPULATION	Patients aged ≥ 21 years, but ≤ 75 years diagnosed with clinically definite, clinically probable, or clinically probable-laboratory supported Amyotrophic Lateral Sclerosis (ALS).
STUDY DESIGN	A phase I/II, open label, single center study designed to assess the safety and tolerability of intramuscular injections of VM202 in patients with ALS. Study enrollment will be staged. Enrollment will be halted after the sixth subject qualifies for treatment. A Data Safety Monitoring Board (DSMB) will conduct a safety evaluation after the first patient treated completes the Day 60 follow-up evaluation and the five other sequentially enrolled subjects complete at least the Day 30 follow-up. Enrollment will be suspended until a formal recommendation to proceed (or not proceed) is made by the DSMB.
NUMBER OF SUBJECTS	18
INCLUSION CRITERIA	1. Age ≥ 21 years, but ≤ 75 years 2. Subjects diagnosed with: • clinically definite ALS, • clinically probable ALS, or • clinically probable-laboratory supported ALS as specified in the revised El Escorial / Airlie House diagnostic criteria 3. Onset of ALS < 2 years at Screening 4. Forced Vital Capacity (FVC) ≥ 60% of predicted 5. Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) ≥ 30 6. Not taking riluzole, or on a stable dose for at least thirty days prior to Screening (defined as no noted toxicities) 7. Able and willing to give informed consent 8. If female of childbearing potential, negative urine pregnancy test at Screening and using acceptable method of birth control during the study.
EXCLUSION CRITERIA	1. Neurological symptom(s) due to vitamin B12 deficiency

2. Requires tracheotomy ventilation or noninvasive ventilation > 16 hours / day
3. Comorbidities such as Parkinson‘s disease, schizophrenia, renal failure, or any other severe complication that, in the Investigator‘s opinion, will compromise the safety of the patient or confound interpretation of the data collected in this study
4. Other neuromuscular disease
5. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger‘s disease)
6. Active infection
7. Chronic inflammatory disease (*e.g.*, Crohn‘s disease, rheumatoid arthritis)
8. Positive HIV or HTLV at Screening
9. Active Hepatitis B or C as determined by Hepatitis B core antibody (HBcAb), antibody to Hepatitis B surface antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV) at Screening
10. Subjects with known immunosuppression or currently receiving immunosuppressive drugs, chemotherapy or radiation therapy
11. Stroke or myocardial infarction within last 3 months
12. Patients with a recent history (< 5 years) of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence);
13. Subjects requiring > 81 mg daily of acetylsalicylic acid; subjects may be enrolled if willing/able to switch to ≤ 81 mg daily of acetylsalicylic acid or to another medication
14. Subjects requiring regular COX-2 inhibitor drug(s) or non-specific COX-1/COX-2 inhibiting drugs, or high dose steroids (excepting inhaled steroids); subjects may be enrolled if willing/able to undergo medication wash-out prior to the first dosing and to refrain from taking these drugs for the duration of the study
15. Have used an investigational drug within 30 days of Screening
16. Pregnant or currently lactating
17. Major psychiatric disorder in past 6 months
18. Known drug or alcohol dependence or any other factors which will interfere with the study conduct or interpretation of the results or who in the opinion of the Investigator are not suitable to participate.

SCREENING

Screening will include assessment of study eligibility, a medical history, vital signs, physical exam, concomitant medications, 12 lead EKG, viral screening, FVC, ALSFRS-R, serum chemistry and hematology, and urine pregnancy test (for women of childbearing potential only).

PRE-INJECTION EVALUATIONS

Prior to injections on Day 0, subjects will be assessed using the ALSFRS-R, the Medical Research Council (MRC) scale for muscle strength testing, dynamometry, FVC, and muscle circumference. These tests can be conducted one day before the scheduled injection visit. Immediately before injection on Day 0, the following will be conducted: recording of concomitant medications, vital signs, and blood draw for serum chemistry and hematology, serum HGF and copies of VM202 in whole blood.

INJECTIONS

VM202 is delivered in 0.5 mL intramuscular injections of a solution of 0.5 mg VM202 / mL. It will be administered over the course of four visits: Day 0, Day 7, Day 14, and Day 21. As in all previous VM202 studies, final dose of VM202 for each target muscle group is divided and administered 2 weeks apart. However, in order to reduce the injection burden on the ALS patient, injection of the upper limbs will be done on separate visits from injection of the lower limbs. The first eligible subject will begin with the lower limb injection series and will be injected in accordance with the schedule outlined in Table 1. The next sequentially eligible patient will begin with injection of the upper limbs (see Table 2). Subsequent eligible patients will be treated in an alternating fashion, such that 9 patients will have initiated their VM202 injections in the lower limbs and 9 patients will have initiated their VM202 injections in the upper limbs. ***Please note: Regardless of injection order, all subjects will receive the same final dose of VM202 and the same number of injections per muscle group.***

Table 1. Group 1 Injection Schedule

TARGET AREA	DOSE VM202 (mg) / TARGET MUSCLE, (NUMBER OF INJECTIONS / MUSCLE GROUP / SIDE (R/L))				TOTAL DOSE (TOTAL NUMBER OF INJECTIONS (R + L))
	DAY 0	DAY 7	DAY 14	DAY 21	
Hand					
Abductor pollicis brevis (APB)		1, (2/2)		1, (2/2)	2, (8)
first dorsal interosseous (FDI)		1, (2/2)		1, (2/2)	2, (8)
Upper Arms					
Biceps		4, (8/8)		4, (8/8)	8, (32)
Deltoid		4, (8/8)		4, (8/8)	8, (32)
Lower Arms					
Extensor carpi radialis		1, (2/2)		1, (2/2)	2, (8)
Flexor carpi ulnaris		1, (2/2)		1, (2/2)	2, (8)
Flexor carpi radialis		1, (2/2)		1, (2/2)	2, (8)
Legs					
Quadriceps	10, (20/20)		10, (20/20)		20, (80)
Gastrocnemius	6, (12/12)		6, (12/12)		12, (48)
Tibialis anterior	3, (6/6)		3, (6/6)		6, (24)
Final Dose (# of injections (L + R))	19 (76)	13 (52)	19 (76)	13 (52)	64 (256)

Table 2. Group 2 Injection Schedule

TARGET AREA	DOSE VM202 (mg) / TARGET MUSCLE, (NUMBER OF INJECTIONS / MUSCLE GROUP / SIDE (R/L))				TOTAL DOSE (TOTAL NUMBER OF INJECTIONS (R + L))
	DAY 0	DAY 7	DAY 14	DAY 21	
Hand					
abductor pollicis brevis (APB)	1, (2/2)		1, (2/2)		2, (8)
first dorsal interosseous (FDI)	1, (2/2)		1, (2/2)		2, (8)
Upper Arms					
Biceps	4, (8/8)		4, (8/8)		8, (32)
Deltoid	4, (8/8)		4, (8/8)		8, (32)
Lower Arms					
Extensor carpi radialis	1, (2/2)		1, (2/2)		2, (8)
Flexor carpi ulnaris	1, (2/2)		1, (2/2)		2, (8)
Flexor carpi radialis	1, (2/2)		1, (2/2)		2, (8)
Legs					
Quadriceps		10, (20/20)		10, (20/20)	20, (80)
Gastrocnemius		6, (12/12)		6, (12/12)	12, (48)
Tibialis anterior		3, (6/6)		3, (6/6)	6, (24)
Final Dose (# of injections (L + R))	13 (52)	19 (76)	13 (52)	19 (76)	64 (256)

OTHER STUDY PROCEDURES / EVALUATIONS

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 7, immediately pre-treatment on Day 14, immediately pre-treatment on Day 21, on Day 30, Day 60 and Day 90.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post last injection), at Day 7 (pre-injection, and 2 hours [± 1 hour] post last injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post last injection), at Day 21 (pre-injection, and 2 hours [± 1 hour] post last injection), on Day 30, Day 60 and Day 90.

ALSFRS-R, FVC and muscle strength (as determined by using the MRC scale) will be assessed at Day 30, Day 60, Day 90, at 6 months and 9 months. Muscle circumference and dynamometry will be conducted on Day 60, Day 90, at 6 months, and 9 months.

A Data Safety Monitoring Board (DSMB) will monitor patient safety throughout the study.

SCHEDULE OF EXAMINATIONS	Screening (Day -30 to Day 0) Day 0 Day 7 ± 1 days Day 14 ± 1 days Day 21 ± 1 days Day 30 ± 3 days Day 60 ± 3 days Day 90 ± 7 days Month 6 ± 1 month Month 9 ± 1 month Subjects will be followed up at 12, 18, 24, and 36 months (1 ± month) by phone to assess survival.
STUDY ENDPOINTS	The primary study endpoint is to evaluate safety and tolerability of intramuscular injections of VM202 at different injection sites in subjects with ALS. Secondary endpoints include the assessment of the neuroprotective potential of VM202.
SAFETY	Adverse events (including serious adverse events, and adverse events leading to treatment discontinuation) throughout the 9 months follow-up will be described according to severity and to their relationship with the study drug and injection procedure. Descriptive statistics will be used to characterize safety parameters.
PHARMACOKINETICS & PHARMACODYNAMICS	HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 7, immediately pre-treatment on Day 14, immediately pre-treatment on Day 21, on Day 30, Day 60 and Day 90. The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 7 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 21 (pre-injection, and 2 hours [± 1 hour] post injection), on Day 30, Day 60 and Day 90.
EFFICACY	This study is not powered to detect differences in efficacy measures. However, descriptive statistics (N, mean, median, SD, minimum and maximum values, where applicable) of clinically meaningful endpoints will be tabulated. Endpoints will include, but are not limited to the following: • ALSFRS-R scale • Muscle circumference • Forced vital capacity • Dynamometry (finger pinch, grip strength and extension of lower leg)

- Muscle strength as evaluated by the MRC scale – scoring only of the subset of muscles specifically injected in this study.

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ABBREVIATIONS

AE / SAE	Adverse Event / Serious Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Transaminase (SGPT)
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
Anti-HCV	Hepatitis C antibodies
AST	Aspartate Transaminase (SGOT)
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulation
CLI	Critical Limb Ischemia
cm	Centimeter(s)
CRF	Case Report Form
CRO	Clinical Research Organization
Cu/Zn	Copper/Zinc
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EAAT2	Excitatory amino acid transporter 2
EKG	Electrocardiogram
ER	Endoplasmic Reticulum
FDA	Food and Drug Administration
GDNF	Glial cell line-derived neurotrophic factor
HBV	Hepatitis B Virus
HBcAb	Hepatitis B core antibody
HBsAb	Antibody to Hepatitis B surface antigen (IgG and IgM)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HTLV	Anti-Human T-Cell Lymphotropic Virus
IND	Investigational New Drug
LLOQ	Lower limit of quantitation
MCP-1	Monocyte chemoattractant protein 1
NGF	Nerve growth factor
NMDA	N-Methyl-D-aspartate
NO	Nitric Oxide
PGE2	Prostaglandin E2
RNA	Ribonucleic Acid
ROS	Reactive oxygen species
SBP	Systolic Blood Pressure
SGPT	Serum Glutamic Pyruvic Transaminase (same as ALT)
TAF	Treatment Authorization Form
TNF	Tumor necrosis factor
SOP	Standard Operating Procedure
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell Count
WFI	Water for Injection

PERSONNEL AND FACILITIES

STUDY SPONSOR

ViroMed Co., Ltd dba VM BioPharma

[redacted]

MEDICAL MONITOR

[redacted]

INVESTIGATORS

John A. Kessler, M.D.
Chairman, Davee Department of Neurology, Davee Professor of Stem Cell Biology, Director, Feinberg Clinical Neuroscience Institute, Director, Northwestern University Stem Cell Institute
303 East Chicago Avenue
Chicago, Illinois 60611-3008

CRO

[redacted]

1. 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, and paralysis. Pathologically, ALS is characterized by progressive degeneration and loss of motor neurons in the spinal cord, brainstem, and cerebral cortex. Death usually occurs within 2–5 years of symptoms onset, most commonly due to respiratory failure. While the majority of ALS cases are sporadic (primary or idiopathic), about 5 – 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]

The incidence of ALS is 1-2 per 100,000 people. It is estimated that as many as 30,000 Americans may have the disease at any given time, but less than 6,000 are diagnosed annually. There is no effective treatment for ALS. The only drug currently approved by FDA for the treatment of this disease is a glutamate release inhibitor (Rilutek, generic: riluzole), which also interferes with N-methyl-D-aspartate (NMDA) receptor mediated events. Its effect is both minimal and controversial.[4]

1.1. PATHOPHYSIOLOGY

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.[5-10] Toxicity results from a combination of damage incurred directly within motor neurons and through damage incurred by nonneuronal 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 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 RNA processing which, together with overproduction of reactive oxygen species (ROS), contribute to aberrant protein folding. Aberrant proteins can form aggregates, leading to proteasome impairment and endoplasmic reticulum (ER) stress. The resulting mitochondrial impairment and dysregulation of calcium handling trigger autophagy and the apoptotic cascade. [11,12] The process is _œontagious‘ and self-perpetuating, affecting the dynamics of cell death in neighboring cells due to release of interleukin-1β, TNF-α, and free radicals.[13] Figure 1 depicts the molecular processes involved in motor neuron injury in ALS.

Figure 1. Molecular mechanisms of motor neuron injury in ALS
from: Ferraiuolo, L., J. Kirby, et al. (2011)[12]

The caspase family. Regardless of the underlying metabolic pathway to degeneration, the end result in ALS is motor neuron death. The major executioners in the apoptotic process are proteases known as caspases (cysteine-dependent, aspartate-specific proteases). Caspases directly and indirectly orchestrate the morphologic changes of the cell during apoptosis. They exist as latent precursors, which, when activated, initiate the death program by destroying key components of the cellular infrastructure and activating factors that mediate damage to the cells.

The first evidence of the role of caspases in a neurodegenerative disease came from experiments in which the "ALS mouse" (SOD^{G93A}) was cross-bred with a mouse expressing a mutant caspase 1 gene that inhibited caspase 1 in neurons. Mice expressing the mutant SOD1 transgene *and* the mutant caspase 1 transgene survived 9% longer, and disease progression was slowed by more than 50 percent.[14] Caspase inhibition in the same model was found to be neuroprotective and extended survival by 22%.[15]

The clinical relevance of these studies is supported by findings in ALS patients. Early activation of caspase-1 in ALS contributes significantly to toxicity.[16] However, neuronal death only occurs following upregulation and concomitant expression of

caspase-3.[17,18] A therapy that could block the upregulation of caspases could potentially improve survival and quality of life of ALS patients.

1.2. CURRENT TREATMENT OPTIONS

Rilutek, (originally manufactured by Sanofi Aventis and approved as an orphan drug on December 12, 1995 (NDA 020599)), is now off-patent and available in the generic form of riluzole. Rilutek was approved on the basis of two controlled trials in which the time to tracheostomy or death was longer for patients randomized to Rilutek than for those randomized to placebo. These studies admitted patients with either familial or sporadic ALS, disease duration of less than 5 years, and a baseline forced vital capacity greater than or equal to 60%. In one study, performed in France and Belgium, 155 ALS patients were followed for at least 13 months (maximum duration 18 months) after being randomized to either 100 mg/day (given 50 mg BID) of Rilutek or placebo. The second study was conducted in both Europe and North America. 959 ALS patients were followed for at least 1 year (North American centers) and up to 18 months (European centers) after being randomized to either 50, 100, 200 mg/day of Rilutek or placebo. The studies concluded that Rilutek extends early survival and / or time to tracheostomy, but there was no statistically significant difference in mortality at the end of the studies.

1.3. UNMET CLINICAL NEED

Riluzole does not prevent or correct the underlying causes of ALS. It has not been shown to improve muscle strength or neurological function. Clearly, a therapy that could impede or reverse neurodegeneration is needed for patients with ALS.

1.4. HGF FOR THE 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.[19-22] HGF stimulates DNA, RNA and protein synthesis by endothelial cells in a dose-dependent manner, upregulates vascular endothelial growth factor (VEGF) expression, and exhibits greater mitogenic activity than that of VEGF alone in human aortic endothelial cells *in vitro*.[21,23-25]

Although largely thought of as an angiogenic agent, HGF has been recently identified as a neurotrophic factor.[26-32] 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. W. 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.[33] It suppresses microgliosis and astrocytosis, which contribute to motor neuron degeneration by producing cytotoxic cytokines and eventual glial scar formation.[33-36]

Early in the disease, surviving nerve fibers establish connections and reinnervate motor units (muscle groups) that have lost their connection to axons that have died. As a result, larger motor units are formed. HGF may be able to slow disease progress by facilitating reinnervation. 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).[37]

HGF may also have protective effects against excitotoxic injuries, because it has been shown to attenuate axonal degeneration by reducing over-excitation (excitotoxicity) through modulation of the expression of the scaffolding protein of the NMDA receptor at the synapse.[38]

Finally, HGF may stave off cell death and halt the cascade of neighboring cell damage by inhibiting caspase signaling.[38,39] In ALS patients, chronic, sublethal activation of caspase appears to mediate cell dysfunction, which precedes cell death.[15,16] 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.[40] Figure 2 depicts the action of HGF on motor neurons. HGF binds to c-Met on cell surface and induces autophosphorylation of the intracellular tyrosine residues of c-Met. Subsequently, HGF inhibits caspase-1 activation, induces XIAP and inhibits its downstream caspases, caspase-3, -7 and -9, thereby effectively dampening caspase-dependent cascades. Therefore, the neurotrophic action of HGF on motor neurons is, at least in part, promoted by preventing caspase-mediated cell death signals.

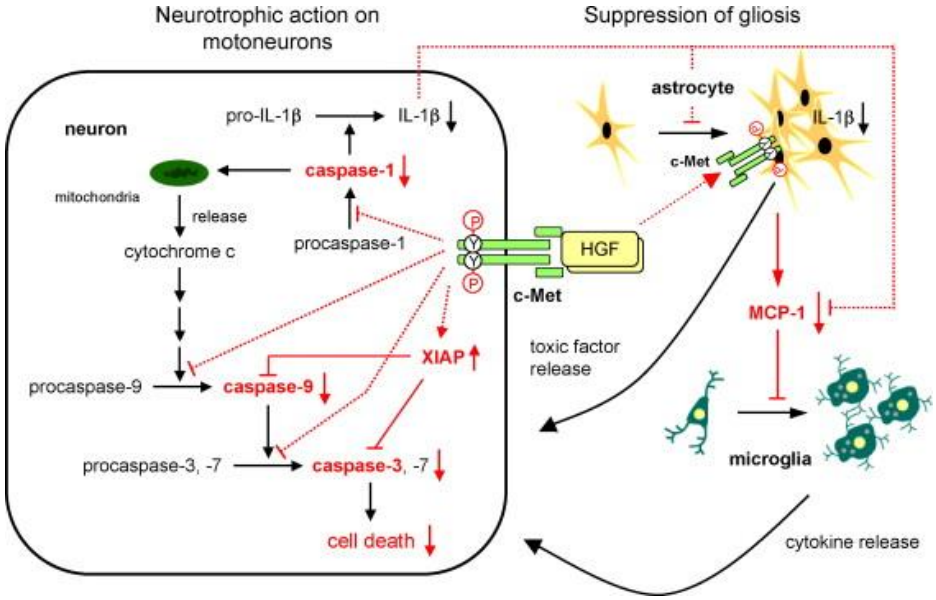

Figure 2. Molecular mechanisms of the neuroprotective effects of HGF
from: Kadoyama, K., H. Funakoshi, et al. (2007)[36]

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.[41,42]

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.

1.5. VM202

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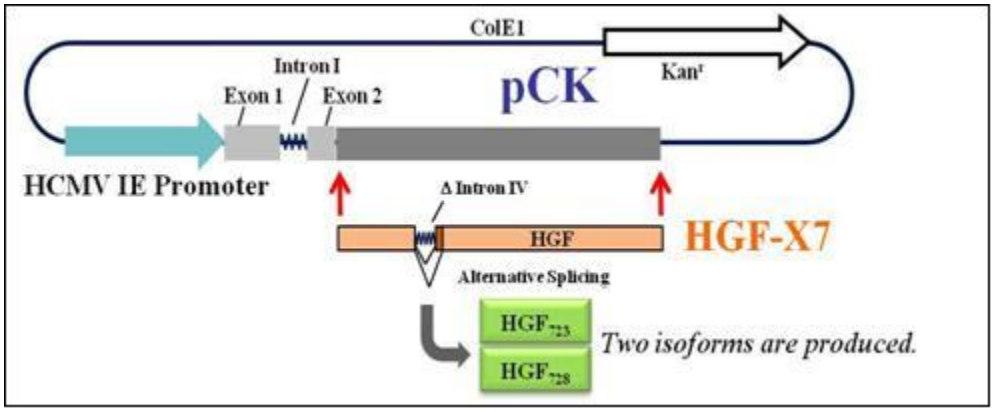

[redacted]

Safety of VM202. The use of plasmids for targeted delivery of angiogenic factors into muscle tissue is a particularly attractive and a relatively safe therapeutic approach, because plasmids have been shown to effectively transfect postmitotic cells such as skeletal and heart muscle and to successfully express angiogenic genes with very little dissemination and persistence at distant sites. Following intramuscular injection, the plasmid that persists is extrachromosomal and integration into host DNA, if it occurs, is negligible.[43-45] This local effect of conventionally injected naked plasmid DNA is well known.[46,47]

Potential Efficacy of VM202. VM202 has demonstrated potential for stimulating angiogenesis in animal models. Its ability to transfect skeletal muscle and produce HGF locally at the site of injection may help support nerve health, regeneration and to forestall motor neuron die-off.

1.6. PRECLINICAL DATA

The non-clinical safety of VM202 has been evaluated for general toxicity following single intramuscular and intravenous doses in rats. In addition, the general toxicity of VM202 following multiple intermittent (weekly or monthly) intramuscular doses has been evaluated in rabbits and rats, respectively. 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 intramuscular administration with or without adjuvant in mice. All species utilized for these studies (mouse, rat, and rabbit) were shown in *in vivo* experiments to be able to express the plasmid following intramuscular injection.

[redacted]

[redacted]

Therefore, the nonclinical efficacy and safety studies support the clinical investigation of VM202 in subjects with amyotrophic lateral sclerosis.

1.7. CLINICAL DATA

VM202 was/is being evaluated in four clinical trials.

1.7.1. PHASE I STUDY IN CRITICAL LIMB ISCHEMIA

[redacted]

[redacted]

[redacted]

Median ABI and TBI significantly increased from 0.35 to 0.52 (P=0.005) and 0.15 to 0.24 (P=0.01*)* at 12 months follow-up. $TCPO_2$ showed an improvement trend (increase). A significant reduction in pain was reported by nine of eleven subjects, with median VAS decreasing from 58 to 16 (P=0.03) at 6 months follow-up. VAS score reduction tracked well with the hemodynamic data.

In general, there was more improvement over baseline in Cohort II (4 mg VM202) than in any other cohort. Cohort I (2 mg of VM202) also experienced a significant reduction in pain and modest improvement in hemodynamic measurement. Interestingly, 2 subjects in each of these cohorts had diabetes, possibly suggesting some benefit of VM202 in this subpopulation. Doses of aspirin above 81 mg daily may have an inhibitory effect on the therapeutic activity of VM202. Results from this study have been published in *Gene Therapy* in 2011.[48]

1.7.2. PHASE II STUDY IN CRITICAL LIMB ISCHEMIA

[redacted]

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[redacted]

1.7.3. PHASE I/II STUDY IN PATIENTS WITH PAINFUL DPN

[redacted]

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1.7.4. PHASE II STUDY IN PATIENTS WITH PAINFUL DPN

[redacted]

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[redacted]

Preliminary Conclusions. These early data support the feasibility and safety of intramuscular injections of VM202 in subjects with critical limb ischemia and DPN. Results suggest that this therapeutic approach may improve functional outcomes and provide symptomatic relief. VM202 is rapidly eliminated from circulation, and appears to remain active only at the injection site. Considering the potential benefit of targeted delivery of HGF to motor neurons in patients with ALS, study of VM202 in this population is warranted.

1.8. STUDY AND DOSE RATIONALE

The natural history of ALS is characterized by unremitting deterioration of neuromotor function. Deterioration rates and patterns vary, with death occurring as rapidly as 1–2 years, but more commonly, within 3-5 years of initial diagnosis. For the majority of patients, symptoms begin with limb involvement. Symptoms may first manifest in the upper or lower limbs first, but regardless of the order in which muscle wasting occurs, the disease is progressive, self-perpetuating, and ultimately results in significant atrophy and weakness in all limbs. We therefore propose treating both upper and lower limbs.

The proposed final (cumulative) dose to be administered to each subject is 64 mg VM202. A dosing schedule similar to the one used in the phase I and the phase II DPN studies will be used in this study. Namely, intramuscular injections for each target muscle group will be divided into two injection visits, (equal halves), two weeks apart. As in all four prior studies, VM202 will be delivered in a solution of 0.5 mg VM202 / mL. The proposed dose is well within that supported by the body of pharmacology and toxicology safety studies of VM202. Safety studies in rabbit, rat and mouse models demonstrate that doses of up to approximately 12.8 times the cumulative clinical dose proposed in this study are safe and resulted in no toxicities. The dose to each muscle group (VM202 is only active once transfected into skeletal muscle cells) falls within the doses given in the four other clinical studies. The excellent safety profile of VM202 seen thus far in the phase I and phase II CLI studies, the phase I/II study in patients with DPN, and from the ongoing phase II DPN study supports this dosing scheme.

2. GOOD CLINICAL PRACTICES (GCP) STATEMENT

This trial will be conducted in compliance with all applicable federal regulations pertaining to investigational drugs and devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 312, and GCP standards. This trial will be conducted in compliance with the protocol as approved by the Institutional Review Board (IRB) and the Institutional Biosafety Committee (IBC) at the study site. Any deviations from the protocol that may affect the safety and welfare of study participants will be immediately reported to the Sponsor and to the IRB and IBC per the institution‘s guidelines.

3. INVESTIGATIONAL PLAN

3.1. STUDY OBJECTIVES

The objective of this Phase I/II study is to evaluate the safety and tolerability of IM administration of VM202 at different injection sites in subjects with ALS.

3.2. STUDY DESIGN

This is a phase I/II, open label, single center study designed to assess the safety and tolerability of intramuscular injections of VM202 in patients with ALS. Subjects with ALS will be screened for study eligibility after giving informed consent.

Screening. Using the revised El Escorial / Airlie House diagnostic criteria and medical history, subjects will be confirmed as having ALS < 2 years. If applicable, the subject will be washed out of prohibited medication (see section 3.4.4). During medication wash-out, screening procedures consisting of assessment of study eligibility, a medical history, vital signs, physical exam, concomitant medications, ALSFRS-R, viral screening, 12 lead EKG, FVC, serum chemistry and hematology, and (urine) pregnancy test (for women of childbearing potential only) will be performed.

All screening assessments should occur within the 30 days prior to Day 0 (day of first injections).

Injection. Prior to injections on Day 0, subjects will be assessed using the ALSFRS-R, the Medical Research Council (MRC) scale for muscle strength testing, dynamometry, FVC, and muscle circumference. These tests can be conducted one day before the scheduled injection visit. Immediately before injection on Day 0, the following will be conducted: recording of concomitant medications, vital signs, and blood draw for serum chemistry and hematology, serum HGF and copies of VM202 in whole blood.

VM202 will be delivered in 0.5 mL intramuscular injections of a solution of 0.5 mg VM202 / mL. It will be administered over the course of four visits: Day 0, Day 7, Day 14, and Day 21. As in all previous VM202 studies, final dose of VM202 for each target muscle group is divided and administered 2 weeks apart. However, in order to reduce the injection burden on the ALS patient, injection of the upper limbs will be done on separate visits from injection of the lower limbs. The first eligible subject will begin with the lower limb injection series and will be injected in accordance with the schedule outlined in Table 3. The next sequentially eligible patient will begin with injection of the upper limbs (see Table 4). Subsequent eligible patients will be treated in an alternating fashion, such that 9 patients will have initiated their VM202 injections in the lower limbs and 9 patients will have initiated their VM202 injections in the upper limbs. ***Please note: Regardless of injection order, all subjects will receive the same final dose of VM202 and the same number of injections per muscle group.***

Table 3. [redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Group 2 Injection Schedule

	DOSE VM202 (mg) / TARGET MUSCLE,	
[redacted]		
i [redacted]		

[redacted]

[redacted]

Serum chemistry and hematology will be determined on Day 0, Day 30, Day 90 and 9 months.

FVC, ALSFRS-R, and muscle strength (MRC scale) will be assessed at Day 0, Day 30, Day 60, Day 90, at 6 months and 9 months. Muscle circumference and dynamometry will be ascertained on Day 0, Day 60, Day 90, at 6 months, and 9 months.

Concomitant medications and vital signs will be recorded throughout the 9 month follow-up period. Adverse events will be assessed starting on Day 0 throughout the 9 month follow-up period, and injection site reactions will be assessed starting on Day 0 through Day 60. Study enrollment will be staged. Enrollment will be halted after the sixth subject qualifies for treatment. A Data Safety Monitoring Board (DSMB) will conduct a safety evaluation after the first patient treated completes the Day 60 follow-up evaluation and the five other sequentially enrolled subjects complete at least the Day 30 follow-up. Enrollment will be suspended until a formal recommendation to proceed (or not proceed) is made by the DSMB.

The study will be suspended pending DSMB review if any of the following SAEs are attributed to VM202 injections during any time during the study:

- acute anaphylaxis (including erythema, hives, wheezing, stridor or respiratory distress);
- temperature >102ºF with negative blood cultures within 24 hours of study drug administration; or
- evidence of active tissue necrosis at the injection site within two weeks of study drug administration.

A summary of the schedule of evaluations and study visits can be found in Appendix 1.

3.3. SUBJECT POPULATION

Eighteen (18) evaluable subjects with ALS meeting the following study entry criteria will be enrolled.

3.3.1. INCLUSION CRITERIA

Subjects must satisfy all of the following criteria to be included in the study:

1. Age ≥ 21 years, but ≤ 75 years
2. Subjects diagnosed with:
   - clinically definite ALS,
   - clinically probable ALS, or
   - clinically probable-laboratory supported ALS;

   as specified in the revised El Escorial / Airlie House diagnostic criteria
3. Onset of ALS < 2 years at Screening;
4. Forced Vital Capacity (FVC) ≥ 60% of predicted;
5. Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) ≥ 30;
6. Not taking riluzole, or on a stable dose for at least thirty days prior to Screening (defined as no noted toxicities);
7. Able and willing to give informed consent;
8. If female of childbearing potential, negative urine pregnancy test at Screening and using acceptable method of birth control during the study.

3.3.2. EXCLUSION CRITERIA

Subjects ***will not be eligible for the study*** if any of the following criteria are present:

1. Neurological symptom(s) due to vitamin B12 deficiency;
2. Requires tracheotomy ventilation or noninvasive ventilation > 16 hours / day;
3. Comorbidities such as Parkinson‘s disease, schizophrenia, renal failure, or any other severe complication that, in the Investigator‘s opinion, will compromise the safety of the patient or confound interpretation of the data collected in this study;
4. Other neuromuscular disease;
5. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger‘s disease);
6. Active infection;
7. Chronic inflammatory disease (*e.g.*, Crohn‘s disease, rheumatoid arthritis);
8. Positive HIV or HTLV at Screening;
9. Active Hepatitis B or C as determined by Hepatitis B core antibody (HBcAb), antibody to Hepatitis B surface antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV) at Screening;
10. Subjects with known immunosuppression or currently receiving immunosuppressive drugs, chemotherapy or radiation therapy;
11. Stroke or myocardial infarction within last 3 months;
12. Patients with a recent history (< 5 years) of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence);

13. Subjects requiring > 81 mg daily of acetylsalicylic acid; subjects may be enrolled if willing/able to switch to ≤ 81 mg daily of acetylsalicylic acid or to another medication;
14. Subjects requiring regular COX-2 inhibitor drug(s) or non-specific COX-1/COX-2 inhibiting drugs, or high dose steroids (excepting inhaled steroids); subjects may be enrolled if willing/able to undergo medication wash-out prior to the first dosing and to refrain from taking these drugs for the duration of the study;
15. Have used an investigational drug within 30 days of Screening;
16. Pregnant or currently lactating;
17. Major psychiatric disorder in past 6 months;
18. Known drug or alcohol dependence or any other factors which will interfere with the study conduct or interpretation of the results or who in the opinion of the Investigator are not suitable to participate.

3.4. STUDY PROCEDURES

Prior to recruitment of any subjects into the study, written approval of the protocol and informed consent must be obtained from the IRB and IBC (if applicable).

3.4.1. INFORMED CONSENT

The Investigator will explain the study purpose, procedures, and subject‘s responsibilities to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained (Appendix 2). The subject will sign and date the informed consent form. The Investigator will also sign and date the consent form. The original informed consent form will be retained with the subject records; a copy will be provided to the subject.

Following is a detailed list of study visits from screening to final follow-up and the required procedures/tests. Methodologies for specific tests/ procedures are described in Section 0.

3.4.2. SUBJECT IDENTIFICATION

To maintain confidentiality, the subject‘s name should not be recorded on any study document other than the informed consent form. All subjects that give informed consent (sign the informed consent form) will be assigned a unique identifier in the following format: X-YY-ZZZ. X is the site number, YY is the sequential subject ID number, and ZZZ are the subject initials (initials of first name/middle name /last name) or Z-Z (initials of first and last name separated by hyphen, if no middle name). For example, the first subject named John Simon Doe at site 1 will be assigned 1-01-JSD; or if John doesn‘t have a middle name, it would be 1-01-J-D.

3.4.3. SCREENING (DAY -30 TO DAY 0)

Prior to full screening, subjects will give informed consent. If applicable, the subject will be washed out of prohibited medication (see section 3.4.4). Subject eligibility will be assessed as follows:

- Evaluation of Eligibility Criteria
- Medical History
- Physical Exam
- Viral screening – HIV, Anti-Human T-Cell Lymphotropic Virus (HTLV), Active Hepatitis B or C as determined by Hepatitis B core antibody (HBcAb), antibody to Hepatitis B antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV)
- EKG
- Urine pregnancy test (for women of childbearing potential only)
- Concomitant Medications
- Vital Signs, including height
- Serum chemistry and hematology
- FVC
- ALSFRS-R

3.4.4. PROHIBITED CONCOMITANT MEDICATIONS

3.4.4.1. MEDICATION THAT MAY INTERFERE WITH VM202 BIOACTIVITY

COX-1 and COX-2 inhibiting drugs may interfere with the bioactivity of VM202, and are therefore prohibited from use during the study. Other than the maximal 81 mg daily dose of aspirin (acetylsalicylic acid), subjects must agree to not take any of these drugs until completion of the 9 month follow-up visit. The patient needs to be advised that common over the counter medications that are prohibited include: Bayer (> 81mg), Excedrin, Aleve, Advil (motrin, ibuprofen). A more complete list of the excluded medications, including the washout period, can be found in Appendix 3.

3.4.4.2. SCREEN FAILURES

Subjects not meeting all study entry criteria will be designated as a screen failures. End of study procedures will not be performed for these subjects, but their reason for discontinuation will be recorded on Screening Log. Screen failures will be replaced.

3.4.5. TREATMENT AUTHORIZATION

After providing written informed consent, potential study participants will undergo Screening assessments. The site will complete a Treatment Authorization Form (TAF) for subjects determined to be eligible for study participation. The TAF includes the subject identification number, demographic information (gender, date of birth), date of informed consent and indication that the subject meets all inclusion and exclusion criteria. The completed TAF will be faxed to the Sponsor or its designee. The Sponsor or its designee will confirm whether the subject can be treated and assign the Injection Schedule. Upon receipt, the Investigator or designee will

schedule the subject to undergo the study treatment. Note: adherence to this process is mandatory to track enrollment and to confirm initial treatment.

3.4.6. DAY 0 – 1ST INJECTION VISIT

3.4.6.1. PRE-INJECTION (≤ 24 HRS OF INJECTIONS)

- FVC
- ALSFRS-R
- Muscle strength (MRC Scale)
- Muscle circumference
- Dynamometry

3.4.6.2. PRE-INJECTION (≤ 4 HRS OF INJECTIONS)

- Concomitant Medications
- Vital Signs
- Serum Chemistry and Hematology
- Serum HGF
- Copies of VM202 in whole blood

3.4.6.3. 1ST DOSE OF VM202

Patients receiving initial injection in the lower limbs will receive 38 injections (0.5 mL / each injection) in each leg as follows:

- Quadriceps - 20 injections/leg
- Calves – 12 injections/leg
- Tibialis anterior – 6 injections/leg

Patients receiving initial injection in the upper limbs will receive 26 injections (0.5 mL / each injection) in each arm as follows:

Hand:
- abductor pollicis brevis (APB) – 2 injections/hand
- first dorsal interosseous (FDI) – 2 injections/hand

Lower Arms:
- Extensor carpi radialis – 2 injection/arm
- Flexor carpi ulnaris – 2 injection/arm
- Flexor carpi radialis – 2 injection/arm

Upper Arms:
- Biceps – 8 injections/arm
- Deltoid – 8 injections/arm

3.4.6.4. POST-INJECTION (1-3 HRS POST LAST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood (2 hours ± 1 hour post last injection)

- Injection site assessment
- Adverse event assessment

3.4.7. DAY 7 ± 1 DAY – 2ND INJECTION VISIT

3.4.7.1. PRE-INJECTION (≤ 4 HRS OF INJECTIONS)

- Concomitant Medications
- Vital Signs
- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.7.2. 2ND DOSE OF VM202

Patients that received injections in the upper limbs last injection visit (1st injection), will receive 38 injections (0.5 mL / each injection) in each leg as follows:

- Quadriceps - 20 injections/leg
- Calves – 12 injections/leg
- Tibialis anterior – 6 injections/leg

Patients that received injections in the lower limbs last injection visit (1st injection), will receive 26 injections (0.5 mL / each injection) in each arm as follows:

Hand:
- abductor pollicis brevis (APB) – 2 injections/hand
- first dorsal interosseous (FDI) – 2 injections/hand

Lower Arms:
- Extensor carpi radialis – 2 injection/arm
- Flexor carpi ulnaris – 2 injection/arm
- Flexor carpi radialis – 2 injection/arm

Upper Arms:
- Biceps – 8 injections/arm
- Deltoid – 8 injections/arm

3.4.7.3. POST-INJECTION (1-3 HRS POST LAST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood (2 hours ± 1 hour post last injection)
- Injection site assessment
- Adverse event assessment

3.4.8. DAY 14 ± 1 DAY – 3RD INJECTION VISIT

3.4.8.1. PRE-INJECTION (≤ 4 HRS OF INJECTIONS)

- Concomitant Medications
- Vital Signs
- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.8.2. 3RD DOSE OF VM202

Patients that received injections in the upper limbs last injection visit (2nd injection), will receive 38 injections (0.5 mL / each injection) in each leg as follows:

- Quadriceps - 20 injections/leg
- Calves – 12 injections/leg
- Tibialis anterior – 6 injections/leg

Patients that received injections in the lower limbs last injection visit (2nd injection), will receive 26 injections (0.5 mL / each injection) in each arm as follows:

Hand:

- abductor pollicis brevis (APB) – 2 injections/hand
- first dorsal interosseous (FDI) – 2 injections/hand

Lower Arms:

- Extensor carpi radialis – 2 injection/arm
- Flexor carpi ulnaris – 2 injection/arm
- Flexor carpi radialis – 2 injection/arm

Upper Arms:

- Biceps – 8 injections/arm
- Deltoid – 8 injections/arm

3.4.8.3. POST-INJECTION (1-3 HRS POST LAST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood (2 hours ± 1 hour post last injection)
- Injection site assessment
- Adverse event assessment

3.4.9. DAY 21 ± 1 DAY – 4TH INJECTION VISIT

3.4.9.1. PRE-INJECTION (≤ 4 HRS OF INJECTIONS)

- Concomitant Medications
- Vital Signs

- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.9.2. 4TH DOSE OF VM202

Patients that received injections in the upper limbs last injection visit (3rd injection), will receive 38 injections (0.5 mL / each injection) in each leg as follows:

- Quadriceps - 20 injections/leg
- Calves – 12 injections/leg
- Tibialis anterior – 6 injections/leg

Patients that received injections in the lower limbs last injection visit (3rd injection), will receive 26 injections (0.5 mL / each injection) in each arm as follows:

Hand:
- abductor pollicis brevis (APB) – 2 injections/hand
- first dorsal interosseous (FDI) – 2 injections/hand

Lower Arms:
- Extensor carpi radialis – 2 injection/arm
- Flexor carpi ulnaris – 2 injection/arm
- Flexor carpi radialis – 2 injection/arm

Upper Arms:
- Biceps – 8 injections/arm
- Deltoid – 8 injections/arm

3.4.9.3. POST-INJECTION (1-3 HRS POST LAST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood (2 hours ± 1 hour post last injection)
- Injection site assessment
- Adverse event assessment

3.4.10. DAY 30 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- Serum chemistry and hematology
- FVC
- ALSFRS-R
- Muscle strength (MRC scale)
- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.11. DAY 60 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- FVC
- ALSFRS-R
- Muscle strength (MRC Scale)
- Muscle circumference
- Dynamometry
- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.12. DAY 90 ± 7 DAYS

- Concomitant Medications
- Vital Signs
- Serum chemistry and hematology
- FVC
- ALSFRS-R
- Muscle strength (MRC Scale)
- Muscle circumference
- Dynamometry
- Serum HGF
- Copies of VM202 in whole blood
- Adverse event assessment

3.4.13. 6 MONTHS ± 1 MONTH

- Concomitant Medications
- Vital Signs
- FVC
- ALSFRS-R
- Muscle strength (MRC Scale)
- Muscle circumference
- Dynamometry
- Adverse event assessment

3.4.14. 9 MONTHS ± 1 MONTH

- Physical exam
- EKG
- Concomitant Medications

- Vital Signs
- Serum chemistry and hematology
- FVC
- ALSFRS-R
- Muscle strength (MRC Scale)
- Muscle circumference
- Dynamometry
- Adverse event assessment

3.4.15. MONTHS 12, 18, 24, 36 ± 1 MONTH

- Phone call to assess survival

3.5. STUDY COMPLETION

3.5.1. COMPLETED SUBJECTS

Each subject in the study will undergo formal clinical assessments throughout the 9 Month Study follow-up visits. Patients will receive follow-up phone calls at 12, 18, 24, and 36 months to assess survival only.

3.5.2. DISCONTINUED SUBJECTS

Any subject may voluntarily discontinue the study at any time without prejudice. The Investigator may discontinue a subject from the study at any time if (s)he considers that remaining in the study compromises the subject‘s health or the subject is not sufficiently cooperative. In either event, reason(s) for discontinuation should be recorded on the CRF.

Possible reasons for study discontinuation include the following:

- Adverse events (AEs) necessitating discontinuation from the study (pre-treatment)
- The subject is lost to follow-up
- Subject decision
- Investigator decision
- Other reason

The reasons for any subject discontinuation will be specified and recorded on the study completion form of the CRF. Additional subjects may be enrolled if subjects discontinue prior to the 90 day visit.

Subjects discontinued for AE(s) will be followed-up after subject‘s discontinuation until the event is resolved or considered medically stable by the Investigator.

Subjects that withdraw prior to study completion will undergo the following assessments if possible:

1. Concomitant Medications
2. Vital signs
3. Physical exam
4. EKG
5. Serum Chemistry and Hematology
6. Serum HGF if discontinued prior to Day 90
7. Copies of VM202 in whole blood if discontinued prior to Day 90
8. Injection site reaction assessment if discontinued prior to Day 60
9. Adverse Events

In case of a subject lost-to-follow-up, the Investigator must do his/her best to contact the subject (by phone or letter) at least twice. If no response is obtained from the subject, the Investigator is encouraged to contact one of the subject's relatives or his/her general practitioner. Documentation of these contacts must be recorded in the subject medical chart. It can be, for instance, the acknowledgement of receipt of a letter sent to the subject.

3.5.3. PREMATURE STUDY TERMINATION

The Sponsor reserves the right to discontinue the study for any safety, ethical or administrative reason at any time.

3.6. INVESTIGATIONAL DRUG PRODUCT AND ACCOUNTABILITY

3.6.1. INVESTIGATIONAL DRUG PRODUCT

VM202 is a DNA plasmid which contains a novel genomic cDNA hybrid human hepatocyte growth factor (HGF) coding sequence (HGF-X7) expressing two isoforms of HGF, HGF_{728} and HGF_{723}. The key feature of HGF-X7 is that it was designed by inserting a series of intron sequences into certain sites of HGF cDNA so that both isoforms of HGF protein are expressed simultaneously and efficiently as in the human genome. Because there is no change in the coding region of the HGF gene, HGF proteins generated from VM202 are identical to the wild-type human HGF proteins.

The plasmid has 7,377 base pairs, a HCMV enhancer / promoter, a growth hormone polyadenylation terminator sequence, ColEl originator, and the Kanamycin resistance gene, on a pCK backbone.

VM202 is supplied in a sterile glass vial containing 2.5 mg of lyophilized study product. VM202 should be stored in a refrigerator at temperatures between 2^{o} C and 8^{o} C in an appropriately locked room accessible only to the pharmacist, or a duly designated person. Since VM202 does not contain preservatives, opened vials of VM202 and VM202 reconstituted with water for injection (WFI) must be used

within 6 hours when stored at room temperature. VM202 should never be frozen. A complete description of test article administration can be found in Appendix 4.

3.6.2. PRODUCT ACCOUNTABILITY

In accordance with federal regulations (21CFR 312.62), all Investigators are required to keep accurate records showing final disposition of all investigational drugs.

Investigational drugs are to be used only in accordance with this protocol and under supervision of the Study Pharmacist or a duly designated person. The Study Pharmacist or his/her designee will maintain an accurate record of the receipt of the test drug as shipped by the Sponsor / Designee, including the date received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This inventory record must be available for inspection at any time. Copies of this record will be provided to the Sponsor by the Study Pharmacist at the conclusion of the study.

After the study is completed, the Study Pharmacist must account for all drug used, unused and partially used. Unused study medication from the study site will be returned to the Sponsor / Designee as directed in writing by the Sponsor for gross reconciliation.

3.6.3. DOSE AND ADMINISTRATION

VM202 is supplied in a sterile glass vial containing 2.5 mg of lyophilized study product. Before administration, it will be reconstituted with 5 mL of water for injection (WFI) by the study pharmacist for a final VM202 concentration of 0.5 mg / mL. Each reconstituted vial is only to be used for one subject. A complete description of test article administration can be found in Appendix 4.

3.7. PRIOR AND CONCOMITANT MEDICATION

All concomitant medications (taken within 30 days of the first injection) will be recorded on the CRF at each study visit. For each medication taken, the following information will be collected:

- Medication trade name;
- Indication for which the medication was given;
- Dose/strength, route, and frequency of administration;
- Date started and date stopped (or continuation at study exit).

4. EXAMINATIONS AND EVALUATIONS

4.1. EVALUATIONS CONDUCTED AT BASELINE ONLY

4.1.1. MEDICAL HISTORY

A medical history will be obtained at Screening/Baseline. All positive findings will be carefully documented on the CRF. Any new finding discovered during screening and prior to the first study drug administration (Day 0) will be considered to be part of the medical history and will not be recorded as an adverse event.

The Investigator will confirm the diagnosis of ALS using the revised El Escorial / Airlie House diagnostic criteria.

4.1.2. PHYSICAL EXAM

A physical exam will be performed at Screening and at 9 months. The exam will include the following: head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, extremities, lymph nodes, and musculoskeletal, neurological, gastrointestinal, and dermatological systems. Any clinically significant abnormalities should be recorded in the subject‘s CRF.

4.1.3. VIRAL SCREENING

The local laboratory will be responsible for Screening viral testing and assays to include: HIV-1, HIV-2, HTLV, and active HBV and HCV as determined by Hepatitis B core antibody (HBcAb), antibody to Hepatitis B antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV).

4.1.4. 12-LEAD EKG

A 12 lead electrocardiogram (EKG) will be conducted at Screening and at 9 months. The EKG recording will be printed out, and a copy will be placed with subject records. Any (clinically significant) abnormalities will be documented.

4.1.5. PREGNANCY TEST (WOMEN OF CHILDBEARING POTENTIAL ONLY)

For women of childbearing potential, a urine beta human chorionic gonadotropin (β-HCG) test will be performed at Screening. Results of the test must be negative and effective contraception documented. Acceptable methods of contraception include:

- Barrier type devices (*e.g.*, female condom, diaphragm and contraceptive sponge) used only in combination with a spermicide;
- Intrauterine device;
- Oral contraceptive agents;
- Depo-provera (medroxyprogesterone acetate);
- Levonorgestrel implants;

Abstention, the rhythm method and / or contraception by a partner are not considered acceptable methods of contraception.

4.2. EVALUATIONS CONDUCTED THROUGHOUT THE STUDY

4.2.1. CONCOMITANT MEDICATIONS

Concomitant medications will be recorded at Screening and at each visit using the trade name or generic name as described in Section 3.7.

4.2.2. VITAL SIGNS

Vital signs consisting of blood pressure (while subject is sitting), temperature, body weight, heart rate, and respiratory rate will be measured and recorded at Screening and at every visit through the 9 month follow-up. Body weight need only be measured once during injection visits (Day 0, Day 7, Day 14, Day 21). All other vital sign measurements will be made both pre and post injection.

4.2.3. SERUM CHEMISTRY AND HEMATOLOGY

Evaluation of serum chemistry and hematology will be conducted at Screening, Day 0, Day 30, Day 90 and 9 months. Evaluations will be conducted at a local laboratory at each site.

Serum chemistry evaluations will include: calcium, glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, albumin, and total protein.

Hematology evaluations will include: complete blood count (CBC): red blood cells (RBC); hemoglobin (Hgb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets and white blood cells (WBC) with differential. Abnormal readings do not necessarily constitute an adverse event; the results need to be reviewed in the context of the subject‘s health.

Laboratory testing by visit is provided in Appendix 1.

4.2.4. SERUM HGF

Serum HGF will be determined by ELISA at the following follow-up visits: immediately pre-treatment on Day 0, immediately pre-treatment on Day 7, immediately pre-treatment on Day 14, immediately pre-treatment on Day 21, on Day 30, Day 60, and Day 90. A minimum 6 cc blood draw will be taken at each time point. Allow blood to clot for 30 – 60 minutes at room temperature then centrifuge for 10 minutes at 1000 x g. Divide the isolated serum into six (6) equal aliquots of ~0.3 mL each. (0.5mL plastic storage tubes provided). Samples should be labeled with subject ID, draw date, study number and visit interval (*i.e.*, Day 0, 7, 14, 21, 30, 60 or 90). Samples will be maintained in a cooler containing dry ice and then placed in a ≤ -65°C freezer until shipped for analysis. At the request of the Sponsor or its designee, serum HGF samples will be batched with VM202 samples, and shipped in

a special container with temperature tracking recorder to Charles River Laboratories for analysis.

Charles River Laboratories
Preclinical Services Nevada
6995 Longley Lane
Reno, NV 89511
Phone: (775) 682-2079

4.2.5. COPIES OF VM202 IN WHOLE BLOOD

[redacted]

4.2.6. FORCED VITAL CAPACITY

Forced Vital Capacity (FVC) is a pulmonary function test that quantifies the volume of air that can forcibly be blown out after full inspiration. It correlates with survival in ALS.[50] FVC will be determined during Screening, on Day 0 before the treatment (injection), on Day 30, Day 60, Day 90, at 6 months and 9 months. FVC measurement will be performed by trained personnel as recommended for ALS clinical trials using standard techniques in the sitting position and expressed as a percentage of the expected value.[51]

4.2.7. REVISED AMYOTROPHIC LATERAL SCLEROSIS FUNCTIONAL RATING SCALE (ALSFRS-R)

The revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) is a validated rating scale for measuring the global function of patients with ALS.[52] 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 physician 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 of between 0=worst and 48=best. The ALSFRS-R will be conducted at Screening, on Day 0 before the treatment (injection), on Day 30, Day 60, Day 90, at 6 months and 9 months. Details can be found in Appendix 5.

4.2.8. MEDICAL RESEARCH COUNCIL (MRC) SCALE FOR MUSCLE STRENGTH TESTING

The Medical Research Council (MRC) Scale is a validated instrument used in assessing muscle strength. It uses the numeral grades 0 – 5 to characterize muscle strength as follows:

0 - No contraction
1 - Flicker or trace contraction
2 - Active movement, with gravity eliminated
3 - Active movement against gravity
4 - Active movement against gravity and resistance
5 - Normal power

The MRC scale will be used to assess muscle strength in the muscle groups injected with VM202. This assessment will be conducted on Day 0 before the treatment (injection), on Day 30, Day 60, Day 90, at 6 months and 9 months. The muscle groups to be evaluated and the methods of evaluation can be found in Appendix 6.

4.2.9. MUSCLE CIRCUMFERENCE

The muscle circumference of the following groups of muscles will be assessed on Day 0 before the treatment (injection), and on Day 60, Day 90, at 6 months and 9 months. Measurements will be taken bilaterally:

- ***Mid-arm:*** at the midpoint of a vertical line that joins the acromion process to the olecranon process
- ***Mid forearm:*** at the proximal one third point of a vertical line that joins the medial epicondyle to the styloid process of the ulna
- ***Mid-thigh:*** midpoint of a vertical line that joins the anterior superior iliac spine to the superior edge of the patella
- ***Mid-leg:*** at the proximal one third point of a vertical line that joins the fibular head to the lateral malleolus

The procedures for measuring muscle circumference can be found in Appendix 7.

4.2.10. DYNAMOMETRY

Finger pinch force, grip strength, and lower leg extension will be measured using non-AC powered dynamometers manufactured by Hoggan Health Industries, Inc. Data will be collected on the Data Collection Software Package that works with all the Hoggan FET dynamometers. These measurements will be performed on Day 0 before the treatment (injection), Day 60, Day 90, 6 months, and 9 months.

4.2.11. INJECTION SITE REACTION ASSESSMENT

Local injection sites reactions will be assessed on Day 0 post injection, Day 7 pre and post injection, Day 14 pre and post injection, Day 21 pre and post injection, Day 30, and Day 60. Any adverse reaction should be reported as an AE.

5. EVALUATION OF ADVERSE EVENTS

5.1. DEFINITIONS

An Adverse Event (AE) is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational product, whether or not considered causally related to the product.

An untoward medical condition can be symptoms (*e.g.*, nausea, chest pain), signs (*e.g.*, tachycardia, enlarged liver) or clinically significant abnormal results of an investigation (*e.g.*, laboratory findings, electrocardiogram).

Conditions or diseases that are chronic but stable should not be recorded on AE pages of the CRF. In addition, changes in a chronic condition or disease that are consistent with natural disease progression are NOT considered AEs and also should not be recorded on AE pages of the CRF. These medical conditions should be adequately documented on the appropriate page of the CRF (medical history and/or physical examination).

An **adverse reaction** means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‗reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

A **serious adverse event (SAE)** is any untoward medical occurrence which:

- Results in death;
- Is life-threatening;

- Requires inpatient hospitalization (admission to hospital with a stay > 24 hours) or prolongation of hospitalization (note, elective procedures requiring hospitalization are not considered a SAE);
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Additionally, important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when they jeopardize the subject or require medical or surgical intervention to prevent one of the serious outcomes listed above. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse. Medical and scientific judgment must be exercised when classifying events as serious.

Life-threatening means that the subject is, in the view of the Investigator, at immediate risk of death from the AE as it occurred. It does not include an AE which, had it occurred in a more serious form, might have caused death.

Persistent or significant disability/incapacity means that the event resulted in permanent or significant and substantial disruption of the subjects‘ ability to carry out normal life functions.

An **unexpected AE** is an AE, the nature or severity of which is not consistent with the applicable product information (*e.g.*, Investigator Brochure for an unapproved product). Expected means that the event has been previously observed with the test article and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications. It is expected that certain disease states will have reoccurring adverse events some of which may be considered expected over time.

5.2. ASSESSMENT OF AEs

All AEs experienced by study subjects, regardless of severity, which occur between the first study drug administration and the 9 month follow-up visit of the study must be recorded on the AE form provided with the CRF. This will include the following information:

- Description of the AE
- Date of onset
- Duration
- Frequency
- Severity
- Seriousness (yes/no)

- Treatment
- Outcome
- Relationship to study medication, injection procedure and/or underlying disease

All AEs and SAEs must be followed until resolution, or the condition stabilizes. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. The Sponsor or its designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations.

5.2.1. AE CAUSALITY

The study Investigator will determine whether an AE is related or unrelated to study medication, the procedure (intramuscular injection) and / or the underlying disease using the following criteria:

Not related: An adverse event that is not related to the use of the test article or administration procedure.

Possibly related: An adverse event that might be due to the use of the test article or administration procedure. An alternative explanation, *e.g.*, concomitant study product(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded.

Probably related: An adverse event that might be due to the use of the test article or administration procedure. The relationship in time is suggestive. An alternative explanation is less likely, *e.g.*, concomitant drug(s), concomitant disease(s).

Definitely related: An AE that is due to the use of the test article or administration procedure. The event cannot be reasonably explained by an alternative explanation – *e.g.*, concomitant drug(s), concomitant disease(s).

5.2.2. AE INTENSITY

The intensity of the AE/SAE will be defined by the following criteria:

Mild:	The AE is noticeable to the subject but does not interfere with routine activity.
Moderate:	The AE is discomforting and interferes with routine activity.
Severe:	The AE significantly limits the subject‘s ability to perform routine activities despite symptomatic therapy.

5.3. REPORTING/RECORDING OF AES

Throughout the course of the study, all efforts will be made by the Investigator to remain alert to possible AEs. The first concern will be the safety of the subject, and

for providing appropriate medical intervention. The period of observation for collection of AEs starts during the first intramuscular injection procedure (Day 0) until the 9 month follow-up visit. Any AE should be recorded on the appropriate CRF page(s).

5.4. REPORTING / RECORDING OF SAEs

5.4.1. INVESTIGATOR'S RESPONSIBILITY

SAEs will be recorded following the first study drug administration through the 9 month follow-up visit. Any SAE that occurs during this investigation, whether or not related to the study medication, must be reported immediately (within 72 hours) to the Sponsor and MedTech Consultants, Inc., the designated CRO.

Each SAE must be followed with appropriate medical management until resolved or assessed as chronic or stable regardless of whether or not, in the opinion of the Investigator, the event is thought to be related to the study medication.

The Investigator will be required to provide complete information concerning each SAE to the CRO and Sponsor within 5 calendar days of the event. This information must be recorded in the subject's medical record and then transcribed onto the SAE FAX Form. The completed SAE Form (including the Investigator's opinion of the relationship of the SAE to the study medication), copies of related results/reports, consultant report(s), and other relevant information will be faxed and/or mailed to the CRO.

In the event of an SAE leading to hospitalization, every effort will be made by the investigational site to obtain medical records, including a hospital discharge summary. In the event of a fatal AE, documentation of any available postmortem findings, including autopsy, will be provided to the Sponsor or their designee. In any event, the Investigator will provide a narrative summary of circumstances, events related to the death, and cause of death, if known. Any follow-up information obtained must be recorded on an SAE follow-up report form.

The Investigator must comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB), and Institutional Biosafety Committee (IBC) if applicable. Upon receipt from the Sponsor of an initial or follow-up IND Safety Report or other safety information, the Investigator must promptly notify his or her IRB, and IBC (if applicable).

5.4.2. SPONSOR'S RESPONSIBILITY

All AEs and SAEs will be reported on an annual basis to FDA in accordance with the IND regulation (21 CFR Part 312). Per the 2010 FDA Guidance Document for Industry and Investigators —Safety Reporting Requirements for INDs and BA/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.‘

All serious, unexpected adverse reactions and suspected adverse reactions will be reported to FDA and to all participating Investigators as an IND Safety Report within 15 calendar days of the event after the sponsor determines that the suspected adverse reaction qualifies for reporting (21 CFR §312.32). Any unexpected fatal or life-threatening AEs will be reported to the Agency within 7 calendar days after the sponsor‘s initial receipt of the information.

The Sponsor 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 VM202 administration or in the overall conduct of the trial.

6. STATISTICAL METHODS

The objective of this Phase I/II study is to evaluate the safety of IM administration of VM202 in subjects with amyotrophic lateral sclerosis. Sample size estimations were not based on formal statistical hypotheses testing due to the exploratory nature of this Phase I/II study. Hypothesis testing will not be performed on any endpoint.

6.1. PATIENT CATEGORIZATION

Screen Failure - Any patient who was consented and entered into the screening process appropriately, but subsequently did not meet the entry criteria in order to be treated. Patients who fail screening will not be followed for safety or efficacy assessment, and no other study procedures will be performed.

Evaluable Patient - Any patient who received the study drug.

Lost to follow-up - A patient deemed to be lost to follow-up is any patient who received treatment, but who does not complete scheduled study visits to 9 months. This includes those patients who withdraw consent and refuse further study participation and all attempts to contact the patient are deemed unsuccessful.

6.2. STUDY ENDPOINTS

The primary study endpoint is to evaluate safety and tolerability of intramuscular injections of VM202 at different injection sites in subjects with ALS. Secondary endpoints include the assessment of the potential of VM202 to reduce neurodegeneration and muscle wasting as determined by the ALSFRS-R, muscle strength (MRC scale), muscle circumference measurements and dynamometry. FVC will also be tracked and trended.

6.2.1. SAFETY

Any patient who receives VM202 will be included in the safety analysis population. Adverse events, serious adverse events, and adverse events leading to treatment discontinuation will be summarized using descriptive statistics. Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized using n, mean, SD, median, minimum, and maximum values. No statistical testing will be performed.

6.2.2. PHARMACOKINETICS & PHARMACODYNAMICS

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 7, immediately pre-treatment on Day 14, immediately pre-treatment on Day 21, on Day 30, Day 60, and Day 90. The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post last injection), at Day 7 (pre-injection, and 2 hours [± 1 hour] post last injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post last injection), at Day 21 (pre-injection, and 2 hours [± 1 hour] post last injection), on Day 30, Day 60, and Day 90.

6.2.3. EFFICACY

This is a phase I /II study, not powered to detect differences in efficacy measures. However, descriptive statistics of clinically meaningful endpoints will be tabulated. The potential of VM202 to reduce neurodegeneration and muscle wasting will be characterized using the ALSFRS-R, muscle strength (MRC scale), muscle circumference measurements and dynamometry. FVC will also be tracked and trended. Survival will also be recorded.

7. ACCESS TO STUDY DOCUMENTS AND STUDY MONITORING

The Sponsor has designated MedTech Consultants to monitor the progress of this study. The clinical monitor, as a representative of the Sponsor, has the obligation to follow this study closely. In addition to conducting a site visit prior to initiation of enrollment, the clinical monitor will visit the study facilities regularly, and utilize telephone and written communications on an ongoing basis to maintain current knowledge of the study.

During periodic visits to the study site, the monitor will review the source documents used in the preparation of the CRFs to verify the accuracy and completeness of the information contained in those reports in preparation for retrieval. All source documents must contain all information required by the CRF. All data generated during this study and the source documents from which they originated are subject to inspection by the Sponsor or its representatives, the FDA and other regulatory agencies.

Upon completion of the study, the clinical monitor will conduct a final visit (close-out) to the site. The objectives of this visit are to ascertain that all regulatory records and reports

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.

8. QUALITY CONTROL AND ASSURANCE

The Sponsor employees and/or their contracted representatives utilize Standard Operating Procedures (SOP) 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 Good Clinical Practice guidance.

A Quality Assurance audit may be conducted by the Sponsor 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 informed consent forms, a review of CRFs, associated source documents and medical records, a review of regulatory documentation, an assessment of study conduct and protocol compliance, and a review of the investigational drug accountability. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the findings of the audit.

9. INSTITUTIONAL REVIEW BOARD (IRB)

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 assuring that an IRB which complies with the requirements set forth in 21 CFR Part 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 or its designee, 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 or its designee prior to release of study supplies.

FDA/relevant health authority regulations require that all advertisements for subject recruitment be approved by an IRB prior to implementation. The complete text and format must be submitted to the Sponsor or its designee 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. A final report must be provided to the IRB and the Sponsor within 3 months of study completion or termination. This report should include: any deviations from the protocol, the number of participants evaluated, the number of participants who withdrew or were withdrawn and the reasons for withdrawal, any significant adverse events and the Investigator's summation of the study.

10. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)

The site at which this trial is being conducted will ensure that an Institutional Biosafety Committee (IBC) is in place. The IBC will ensure that the site conforms to the requirements set forth in the Section IV-B-2 of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules, promulgated by the National Institutes of Health/Office of Biotechnology Activities (NIH/OBA).

The Investigator will be responsible for petitioning the IBC and obtaining approval prior to enrolling any subject in the study. The Investigator will also be required to obtain and follow all biohazard safety guidelines promulgated by the IBC, and to report all findings as required to the IBC and to NIH/OBA.

If a potential clinical site does not receive any NIH funding (either directly or indirectly) and does not have an institutional IBC, they can participate in the study if they issue a certification statement to that effect. The certification statement will be submitted to the OBA.

11. INFORMED CONSENT PROCESS

It is the responsibility of the Investigator to inform each subject, prior to performing any study-related assessments, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject‘s chart. A sample informed consent form containing the required elements of informed consent is provided in Appendix 2. Any changes made to this sample must be approved by the Sponsor or its designee, prior to submission to the IRB. After approval by the Sponsor or its designee, the informed consent must be submitted to and approved by the IRB. Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign and date the informed consent form. The person executing the consent must also sign and date the final consent form page. The original informed consent form is to be retained by the study site and a copy is to be given to the subject.

The informed consent must be written in a language in which the subject is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language informed consent forms be submitted to the IRB for approval. The Investigator must forward a copy of the consent form, the certified foreign language translation and an IRB approval letter to the Sponsor or its designee.

12. CONFIDENTIALITY

In accordance with GCP and with the national data protection laws, all information concerning the subjects 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 the Sponsor or its designee or developed or acquired in connection with the study are 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 Sponsor in writing. Such consent shall 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, and, 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.

13. PROTOCOL AMENDMENTS

The Sponsor will document modifications to the protocol in the form of a written amendment. Protocol modifications that impact subject safety or the validity of the study must be approved by the IRB before implementation. In the case of a medical emergency, to remove immediate apparent hazard to subjects, a change may be made preferably after discussion with the Sponsor or its designee. In these instances, the IRB and FDA will be notified as soon as possible.

14. DATA MANAGEMENT

All data relating to study procedures will be entered into CRFs provided by the Sponsor or its designee. All requested information must be entered on the CRF. If an item is not available or not applicable this fact should be indicated.

Obvious errors (self-evident corrections) will be corrected and documented by the Sponsor or its designee. Other errors or omissions will result in queries which will be sent to the investigational site on Data Clarification Forms (DCF)/Query Forms for resolution. A copy of the signed DCF is to be kept by the site with the CRFs. Once the original is received by the Sponsor or its designee, the resolutions will be reviewed and entered into the database.

Data will be entered into a computer database developed specifically for this trial. Access to the database will be restricted to personnel responsible for data entry and to data management and statistics personnel who are directly involved in the management or analysis of this trial. During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction.

Prior to database lock, statistical verification of the data will be undertaken in order to further assure data quality.

15. RECORD KEEPING AND RETENTION

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor and its representatives and FDA/relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the Investigator. This information will be treated with strict adherence to professional standards of confidentiality.

An Investigator must in reasonable time, upon request from any properly authorized officer or employee of FDA/relevant health authority or 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 or regulatory agency, the Investigator will contact the Sponsor or its designee immediately. The Investigator will also grant Sponsor representatives the same privileges offered to FDA/relevant health authority or regulatory agents/officers/employees.

The Investigator must provide the Sponsor 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 course of the study any changes occur that are not reflected on the 1572, a new 1572 form must be completed and sent to Sponsor/CRO.
- Current signed curriculum vitae (within 2 years) and current medical licenses for the Principal Investigator and all co-Investigators listed on the 1572.
- A copy of the original approval for conducting the study by the IRB. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy.
- A copy of the IRB approved informed consent form.
- IRB member list and DHHS General Assurance Number (if IRB has an Assurance number).
- Signed Financial Disclosure Form for all personnel listed on the 1572.
- The signature page of this protocol signed and dated by the Principal Investigator.

In addition to the documents listed above, the study site will also retain the following items:

- Certifications and laboratory reference ranges for all local laboratories used for this study.
- All original informed consent forms with required signatures
- All IRB correspondence (*i.e.*, informed consent [including any approved revisions], protocol, AE, advertisements, newsletters)
- Copy of the Study Monitoring Log Sheet

- Clinical and non-clinical supply shipment forms
- Copies of all correspondence pertaining to the study (except budget issues) between the Sponsor or the CRO and the site
- Copies of all SAEs reports submitted to the Sponsor its designee
- Copies of all IND Safety Reports submitted to the site by the Sponsor its designee
- Copies of approved package labeling
- Study personnel signature log

All study-related records must be maintained for at least 2 years after a marketing application (NDA/BLA) is approved for the drug; or if an application is not approved for the drug, until at least 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA/health authorities or regulatory agencies have been notified. The Sponsor will notify the principal Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the principal Investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

16. INVESTIGATOR FINAL REPORT

The Investigator shall provide the IRB and the Sponsor with an accurate final report within 3 months after completion, termination or discontinuation of the study. The final report may not precede retrieval of CRFs which have not been monitored.

17. STUDY REPORT AND PUBLICATION

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

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Appendix 1. Schedule of Evaluations and Visits & Laboratory Tests by Visit

SCHEDULE OF EVALUATIONS AND VISITS

Procedure	Screening / Baseline (-30 – 0 D)	1st Injection Day 0		2nd Injection Day 7 ± 1 D		3rd Injection Day 14 ± 1 D		4th Injection Day 21 ± 1 D		Day 30 ± 3 D	Day 60 ± 3 D	Day 90 ± 7 D	6 M ± 1 M	9 M ± 1 M	12, 18, 24 and 36 M	Withdrawal before 9M Visit
		Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose							
Baseline Evaluation																
Informed Consent	✓															
Medical History	✓															
Physical Exam	✓													✓		✓
Viral screening	✓															
EKG	✓													✓		✓
Urine Pregnancy test	✓															
Safety and Efficacy Parameters																
Concomitant Medications	✓	✓		✓		✓		✓		✓	✓	✓	✓	✓		✓
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Serum Chemistry and Hematology	✓	✓								✓		✓		✓		✓
FVC	✓	✓†								✓	✓	✓	✓	✓		
ALSFRS-R	✓	✓†								✓	✓	✓	✓	✓		
Muscle strength (MRC Scale)		✓†								✓	✓	✓	✓	✓		
Muscle circumference		✓†									✓	✓	✓	✓		
Dynamometry		✓†									✓	✓	✓	✓		
Serum HGF		✓		✓		✓		✓		✓	✓	✓				✓[1]
Copies of VM202 in whole blood		✓	✓*	✓	✓*	✓	✓*	✓	✓*	✓	✓	✓				✓[1]
Treatment																
Injection site reaction assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓					✓[2]
Adverse Events			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Phone call follow-up to assess survival															✓	

† Can be conducted the day before injections
* 2 hours after injection (± 1 hour)
1. If withdrawal occurred before Day 90 Visit
2. If withdrawal occurred before Day 60 Visit

SCHEDULE OF LABORATORY EVALUATIONS

Parameters	Screen	Day 0	Day 7, 14, 21	Day 30	Day 60	Day 90	6 Months	9 Months	Early Withdrawal
Serum HGF		✓ pre-injection	✓ pre-injection	✓	✓	✓			✓ (< Day 90)
VM202		✓ pre & post injection	✓ pre & post injection	✓	✓	✓			✓ (< Day 90)
HTLV, HIV-1, HIV-2	✓								
Hepatitis B and C[†]	✓								
Hematology									
Hematocrit	✓	✓		✓		✓		✓	✓
Hemoglobin	✓	✓		✓		✓		✓	✓
RBC	✓	✓		✓		✓		✓	✓
WBC with differential	✓	✓		✓		✓		✓	✓
Platelets	✓	✓		✓		✓		✓	✓
MCV	✓	✓		✓		✓		✓	✓
MCH	✓	✓		✓		✓		✓	✓
MCHC	✓	✓		✓		✓		✓	✓
Chemistry									
Albumin	✓	✓		✓		✓		✓	✓
Alkaline Phosphatase	✓	✓		✓		✓		✓	✓
ALT	✓	✓		✓		✓		✓	✓
AST	✓	✓		✓		✓		✓	✓
Bicarbonate	✓	✓		✓		✓		✓	✓
BUN	✓	✓		✓		✓		✓	✓
Calcium	✓	✓		✓		✓		✓	✓
Chloride	✓	✓		✓		✓		✓	✓
Creatinine	✓	✓		✓		✓		✓	✓
Glucose	✓	✓		✓		✓		✓	✓
Potassium	✓	✓		✓		✓		✓	✓
Sodium	✓	✓		✓		✓		✓	✓
Total Protein	✓	✓		✓		✓		✓	✓
Total Bilirubin	✓	✓		✓		✓		✓	✓

[†] Hepatitis B core antibody (HBcAb), antibody to Hepatitis B surface antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV)

Appendix 2. Sample Informed Consent

TITLE: A Phase I/II, Open Label Study to Assess the Safety and Tolerability of VM202 in Subjects with Amyotrophic Lateral Sclerosis (Protocol VMALS-001)

SPONSOR: VM BioPharma

[redacted]

PRINCIPAL INVESTIGATOR:	John A. Kessler, M.D. Ken and Ruth Davee Professor of Stem Cell Biology Professor in Ken and Ruth Davee Department of Neurology and Molecular Pharmacology and Biological Chemistry
INSTITUTION:	Northwestern University Stem Cell Institute 303 East Chicago Avenue Chicago, Illinois 60611-3008
SUBJECT INITIALS:	[INSERT SUBJECT'S INITIALS]
SUBJECT NUMBER:	[INSERT SUBJECT'S UNIQUE STUDY NUMBER]

You are being asked to participate in a research study sponsored by VM BioPharma. Before you decide whether to participate, it is important for you to know why the research is being done, and what it will involve. Please take your time to read the following information carefully, and feel free to discuss your decision with your family, friends, and your primary care doctor. Please ask your study doctor to explain if there is anything that is not clear or if you would like more information. If you agree to take part in this study, you need to sign this consent form. Your signature on this form means that you have been told about and understand the purpose of the study, procedures to be followed, and any benefits or risks. Your signature on this form also means that you want to take part in this study if you meet the criteria, based on the results of your medical tests, which must be done before you are asked to continue your participation in the study. After you agree, you will be provided with a copy of this signed form for your records.

Do I have to take part?
Taking part in this study is entirely voluntary, and you may refuse to participate or withdraw from the study at any time without influencing your regular medical treatment and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. Regardless of your decision, you will still be treated for your medical condition.

Why is this research study being done?
You are being considered for participation in this research study because you have been diagnosed with amyotrophic lateral sclerosis (ALS). The specific events that result in ALS are not well understood, but all ALS patients experience damage to the nerve cells in the brain and spinal cord that are responsible for controlling voluntary movement (motor neurons). For unknown reasons, in ALS, these motor neurons stop working. The muscles the motor neuron control no longer function, and they gradually become paralyzed.

Supporting motor neuron health and function may slow down the degenerative processes in ALS. Researchers have discovered that a protein called hepatocyte growth factor (HGF) that your body naturally produces in small amounts can protect nerves. Unfortunately, your body only makes a small amount of this protein and not always in the areas where you need it. Researchers have found a way to increase the amount of HGF in your limbs. They have isolated the genes responsible for directing the production of HGF, and have designed a product that can be injected into your muscles.

In this research study, the HGF gene will be injected into the muscles of your arms, hands, and legs to evaluate if it affects your ALS symptoms and disease progression. The product being used in this study is called VM202. VM202 is an experimental drug that is not yet approved by regulatory authorities (the US Food and Drug Administration [FDA]). VM202 is a plasmid (a small piece of DNA), which includes the genes for HGF. VM202 has been used in two small studies in the United States in patients with painful diabetic neuropathy (another neural degenerative disease); in two small studies in patients with critical limb ischemia, and in a study in Korea in patients with coronary artery disease. VM202 has also been tested in people undergoing coronary bypass surgery. It is hoped that VM202 injected into your muscles will slow down the progression of your ALS symptoms.

Who is in charge of this study?
The Principal Investigator is John A. Kessler, M.D. This study is sponsored and funded by VM BioPharma Co., Ltd. VM BioPharma Co., Ltd. will use a specialized research company, called a contract research organization, in addition to specialized laboratories to manage and execute some parts of the detailed requirements of the study.

How many people will take part in this research study?
A total of 18 patients will take part in this study at Northwestern University.

What happens if I agree to be in this research study?
After you sign this consent form indicating you want to participate in this study, you will need to undergo some tests to see if you qualify for the study. If you do not meet all of the study entry criteria, you will not be able to participate in the study and your doctor will discuss with you other options that you may have for treatment of your medical condition. The study doctor will tell you whether you are able to participate in this study after the initial test results are received and reviewed.

This study is an open label clinical study. All patients will receive the same final dose of VM202 (64 mg). VM202 is delivered by administering small injections into the muscles. Individual injections contain 0.5 ml of fluid with 0.25 mg VM202. This is about one tenth of a teaspoon of fluid per injection.

You will receive VM202 injections four times (every 7 days) after you qualify for the study. Each week, you will alternate between receiving injections in the arms and hands or injections in the legs. In this way, your arms will be treated twice with VM202 and your legs will be treated twice with VM202.

The first eligible patient will begin the injection series with injections in the legs. The next eligible patient will receive initial injections in the arms and subsequently eligible patients will alternate between initiating treatment in the arms or legs. Depending when you qualify, the injections will start in your arms and hands OR in your legs.

When receiving injections in the arms, you will get 26 injections of VM202 distributed over each arm (upper arm, forearm, and hand) for a total of 52 injections (right arm/hand and left arm/hand). When receiving injections in the legs, you will get 38 injections of VM202 distributed over each leg (thigh and calf) for a total of 76 injections (right leg and left leg).

All patients will receive the same final dose of VM202 (64 mg) and the same number of injections in the arms and legs.

What tests, procedures, and diagnostic studies will be done during this study?
There are 10 visits which span 9 months total time from visit #2 to visit #9. Depending on the visit, different tests will be done. Visit #1 may actually take more than one visit to accomplish depending on how many tests can be scheduled on that first day, but is usually completed within a week before the first injection procedure (Visit #2). Below is a detailed description of each of the required visits and the laboratory tests, procedures, and evaluations that will be done during the visits.

Description of the tests, procedures, and diagnostic studies to be done

Medical history – Discussion with your doctor of your medical history, including ALS family history, current symptoms and any changes that have happened.

Physical exam – Your doctor will give you a physical exam and will check your reflexes, strength, balance, and coordination. This exam will also include taking your sitting blood pressure, temperature, heart rate, height and weight (**vital signs**).

Medication Review – Discussion with your doctor of what medications and dietary supplements you have taken or are currently taking. Please note, some medications may not be taken during the study since they may interfere with the potential effect of the study medication or ability to assess the response to the study medication. The doctor will talk to you about these medications; if you are currently taken any of these medications, you will be asked to stop taking these medications for the duration of the study.

Assessment of ALS – Assessment by your doctor of your ALS symptoms.

Injection site reaction assessment – Assessment by your doctor of any pain or other reaction at the locations where VM202 was injected.

Assessment of side effects – Assessment by your doctor of any unpleasant medical experiences, side effects, or discomforts that may have happened to you.

Questionnaire – You and your doctor will fill out a short questionnaire about your ALS symptoms during the screening process and right before the first injections. This questionnaire, (ALS Functional Rating Scale [ALSFRS-R]), asks about your ability to function in certain daily activities. You will be asked to complete this questionnaire again at some visits.

Forced Vital Capacity (FVC) – To test how well your lungs are working, we will measure the greatest amount of air you can exhale (breath out) following a deep breath. For this test, we will ask you to hold a mouthpiece in your mouth, breathe in deeply, and breathe out slowly for as long as you can.

Muscle Strength – The strength in your arms and legs will be evaluated by physical exam using a scoring method (Medical Research Council [MRC] scale). The scale ranges from ‗0' (No contraction) to ‗5' (Normal power). Muscle strength and range of motion will also be measured using a small device called a hand-held dynamometer. The evaluator will hold the device in his or her hand and will push against your arms and legs while you try to hold against this pushing. This testing will take approximately 30 minutes. This should not hurt, but may be slightly uncomfortable due to pressure and may make your muscles tired. You will also be asked to squeeze a hand-held dynamometer to measure the strength of your fingers.

Muscle Circumference – The size of your arm and leg muscles will be measured using a standard, flexible, non-elastic, plastic measuring tape.

Pregnancy test – If you are a female of child bearing age, you will undergo a urine pregnancy test to confirm that you are not pregnant. You cannot participate if you are pregnant or plan to become pregnant during the course of the trial.

12 Lead EKG – An electrocardiogram (EKG) is a measurement of your heart's electrical activity that is traced and sent to a machine, which can be read by your doctor. This procedure is not painful and involves lying as still as possible for a few minutes with sticky pads (electrodes) on your chest, arms and legs which are connected through wires to the EKG machine. This test typically takes approximately 15 to 20 minutes.

Blood tests – Routine blood tests will be done at certain visits. Laboratory tests will also include testing for **VM202** and **HGF** levels in the blood at certain visits. The screening evaluation laboratory tests will include viral tests for various diseases including **HIV** (the AIDS virus), **HTLV** (human T-cell lymphotropic virus), hepatitis B (**HBV**), and hepatitis C (**HCV**).

Following is a list of each visit and the specific tests that will be done.

Visit # 1: Screening/Baseline Evaluations
Screening is a process of evaluating your initial health status and assessing the status of your ALS. Screening is usually completed within one month before the first study injections if you qualify for this study. If you agree to take part in this research study, you will first sign this consent form, and then undergo screening. Screening will involve the following procedures: medical history, physical exam, vital signs, medication review, determination of how well your lungs are working, determination of your ALS status (completion of questionnaire), blood tests including a viral screen; urine pregnancy test (if you are a female of childbearing age), and the 12 lead EKG.

Please note: If any of your viral test results are positive you may need to have a second test to make sure the results are the same. The doctor or his/her nurse will tell you how to find medical help and counseling as needed, and you will not be able to take part in this study. The study Sponsor will not pay for the cost of the repeat tests, or any other follow-up medical care, or counseling for a positive or abnormal test result.

It takes approximately one to two weeks to get all of the initial test results. After your doctor has reviewed the results of these tests he/she will determine whether you are eligible for participation in the study. If you are eligible for the study and you do wish to continue, you will be scheduled for the first set of injections which will be done at your next visit (Visit #2).

Visit # 2 – Day 0 of the Study: First Injection Procedure

Before Injection Procedure:
The following tests will be performed *before* you have your injection procedure done: medication review, vital signs, measurement of lung function (FVC), the ALSFRS-R questionnaire, measurement of muscle circumference, measurement of muscle strength and range of motion, and blood tests including HGF and VM202.

Injection Procedure:
The injection procedure will be done in your doctor‘s office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 at sites evenly distributed over your arm or leg muscles (depending on which series of injections you are assigned to start with). If you are receiving injections in the arms, you will receive 26 injections in each arm as follows:

- Hand – 4 injections in each hand: 2 in the palm in the large muscle under the thumb; 2 in the muscle between the thumb and forefinger
- Forearm - 6 injections in each forearm: 4 on the inside of the forearm, 2 on the outer forearm
- Upper arm – 16 injections in each upper arm: 8 in the biceps, 8 in the deltoids (upper arm / shoulder)

If you are receiving injections in the legs, you will receive 38 injections in each leg as follows:

- Thigh – 20 injections evenly distributed over the front of each thigh
- Calf – 12 injections evenly distributed over the back of each calf, 6 injections on the front of each calf

Each injection will take 3 - 5 seconds. The entire injection procedure is expected to take 30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, injection site reaction assessment, blood tests for VM202, and assessment of side effects.

Before you go home discharge instructions about what you need to do to take care of yourself, what medications you should take, and who to call if you have a problem after you leave the clinic, will be reviewed with you by the nurse and/or doctor. Research personnel will be on call anytime to answer any questions that you may have and respond to reports you may have of any symptoms.

Visit # 3 – Day 7 of the Study: Second Injection Procedure

Before Injection Procedure:
The following tests will be performed *before* you have your injection procedure done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment, and assessment of side effects.

Injection Procedure:
The injection procedure will be done in your doctor‘s office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 at sites evenly distributed over your arm or leg muscles (the limbs not injected in the previous visit). If you are receiving injections in the arms, you will receive 26 injections in each arm as follows:

- Hand – 4 injections in each hand: 2 in the palm in the large muscle under the thumb; 2 in the muscle between the thumb and forefinger
- Forearm - 6 injections in each forearm: 4 on the inside of the forearm, 2 on the outer forearm
- Upper arm – 16 injections in each upper arm: 8 in the biceps, 8 in the deltoids (upper arm / shoulder)

If you are receiving injections in the legs, you will receive 38 injections in each leg as follows:

- Thigh – 20 injections evenly distributed over the front of each thigh
- Calf – 12 injections evenly distributed over the back of each calf, 6 injections on the front of each calf

Each injection will take 3 - 5 seconds. The entire injection procedure is expected to take 30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, injection site reaction assessment, blood tests for VM202, and assessment of side effects.

Before you go home discharge instructions about what you need to do to take care of yourself, what medications you should take, and who to call if you have a problem after you leave the clinic, will be reviewed with you by the nurse and/or doctor. Research personnel will be on call anytime to answer any questions that you may have and respond to reports you may have of any symptoms.

Visit # 4 – Day 14 of the Study: Third Injection Procedure

Before Injection Procedure:

The following tests will be performed *before* you have your injection procedure done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment, and assessment of side effects.

Injection Procedure:
The injection procedure will be done in your doctor‘s office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 at sites evenly distributed over your arm or leg muscles (the limbs not injected in the previous visit). If you are receiving injections in the arms, you will receive 26 injections in each arm as follows:

- Hand – 4 injections in each hand: 2 in the palm in the large muscle under the thumb; 2 in the muscle between the thumb and forefinger
- Forearm - 6 injections in each forearm: 4 on the inside of the forearm, 2 on the outer forearm
- Upper arm – 16 injections in each upper arm: 8 in the biceps, 8 in the deltoids (upper arm / shoulder)

If you are receiving injections in the legs, you will receive 38 injections in each leg as follows:

- Thigh – 20 injections evenly distributed over the front of each thigh
- Calf – 12 injections evenly distributed over the back of each calf, 6 injections on the front of each calf

Each injection will take 3 - 5 seconds. The entire injection procedure is expected to take 30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, injection site reaction assessment, blood tests for VM202, and assessment of side effects.

Before you go home discharge instructions about what you need to do to take care of yourself, what medications you should take, and who to call if you have a problem after you leave the clinic, will be reviewed with you by the nurse and/or doctor. Research personnel will be on call anytime to answer any questions that you may have and respond to reports you may have of any symptoms.

Visit # 5 – Day 21 of the Study: Fourth and Final Injection Procedure

Before Injection Procedure:
The following tests will be performed *before* you have your injection procedure done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment, and assessment of side effects.

Injection Procedure:
The injection procedure will be done in your doctor‘s office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 at sites evenly distributed over your arm or leg muscles (the limbs not injected in the previous visit). If you are receiving injections in the arms, you will receive 26 injections in each arm as follows:

- Hand – 4 injections in each hand: 2 in the palm in the large muscle under the thumb; 2 in the muscle between the thumb and forefinger
- Forearm - 6 injections in each forearm: 4 on the inside of the forearm, 2 on the outer forearm
- Upper arm – 16 injections in each upper arm: 8 in the biceps, 8 in the deltoids (upper arm / shoulder)

If you are receiving injections in the legs, you will receive 38 injections in each leg as follows:

- Thigh – 20 injections evenly distributed over the front of each thigh
- Calf – 12 injections evenly distributed over the back of each calf, 6 injections on the front of each calf

Each injection will take 3 - 5 seconds. The entire injection procedure is expected to take 30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, injection site reaction assessment, blood tests for VM202, and assessment of side effects.

Before you go home discharge instructions about what you need to do to take care of yourself, what medications you should take, and who to call if you have a problem after you leave the clinic, will be reviewed with you by the nurse and/or doctor. Research personnel will be on call anytime to answer any questions that you may have and respond to reports you may have of any symptoms.

Visit # 6 – 1 Month after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests including HGF and VM202, measurement of lung function (FVC), the ALSFRS-R questionnaire, measurement of muscle strength using the MRC scale, injection site reaction assessment, and assessment of side effects.

Visit # 7 – 2 Months after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, measurement of lung function (FVC), the ALSFRS-R questionnaire, measurement of muscle circumference, measurement of muscle strength using the MRC scale, measurement of muscle strength and range of motion using a hand-held dynamometer, and blood tests for HGF and VM202, injection site reaction assessment, and assessment of side effects.

Visit # 8 – 3 Months after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, measurement of lung function (FVC), the ALSFRS-R questionnaire, measurement of muscle circumference, measurement of muscle strength using the MRC scale, measurement of muscle strength and range of motion using a hand-held dynamometer, and blood tests including HGF and VM202, and assessment of side effects.

Visit # 9 – 6 Months after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, measurement of lung function (FVC), the ALSFRS-R questionnaire, measurement of muscle circumference, measurement of muscle strength using the MRC scale, measurement of muscle strength and range of motion using a hand-held dynamometer, and assessment of side effects.

Visit # 10 – 9 Months after the First Injection Procedure
At this visit, the following tests or evaluations will be done: physical exam, 12 lead EKG, medication review, vital signs, measurement of lung function (FVC), the ALSFRS-R questionnaire, measurement of muscle circumference, measurement of muscle strength using the MRC scale, measurement of muscle strength and range of motion using a hand-held dynamometer, blood tests, and assessment of side effects.

Home Visits
If your ALS symptoms worsen after you receive all of your injections and you are unable to come to the clinic for study visits, please let the study staff know. We will do your remaining study visits as ~~h~~home visits."

After you have completed your 9-month follow-up visit, you do not have to return for any more visits. You will receive a call from the study coordinator 12, 18, 24 and 36 months after initial treatment to check on your health.

How long will I be in this research study?
Your last follow up visit will be approximately 9 months, but we will continue to follow your progress for up to 3 years. After the third year phone call, you will have completed this study.

What do I have to do as a participant in this study?
Participation in this study requires you to make sure that you are available to attend all your scheduled visits through 9 months. During your participation in the study you will be asked to report any unpleasant medical experiences that you may have.

You must not use any additional prescription medication before the 9 month study visit without first checking with your study doctor. If you use any non-prescription medication you should inform your doctor of the details (medication, dose, etc.) at each study visit.

You also must not participate in any other clinical trial before the 9 month study visit.

What about my rights to decline participation or withdraw from the study?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care. If you do decide to stop your participation in the study, you should talk to your doctor immediately so he/she can advise you of any additional tests that may be needed for your safety. Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if he/she determines that it is no longer in your best interest to continue. The Sponsor or regulatory agencies may stop this study at any time without your consent. If this occurs, you will be notified and your study doctor will discuss with you other options you may have.

What are the risks of this research study?
There are known risks and discomforts involved in some of the tests and evaluations. There are also unknown risks. Below is a description of these risks. Your doctor will discuss the risks and procedures with you before you start in the study.

Risks from Injection Procedures
VM202 will be injected into your muscles using a fine needle. There may be some pain at the injection site at the time of injection. There may be swelling, bruising or inflammation near the injection site. There may be a risk of an allergic reaction, fever or tissue damage from the injection. Because HGF has the potential to create new blood vessels, there may be risk of promoting tumor growth (cancer) or of increasing the number of blood vessels in the back of your eye and damaging your retina.

Risks to women who can get pregnant or are breastfeeding
Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore, pregnant women cannot take part in this study. If you are a woman who can get pregnant, a urine pregnancy test will be done and it must show that you are not pregnant before

you can participate in this study. You must also agree not to become pregnant during this study. You may not take part in this study if you are breastfeeding. If sexually active and with childbearing potential, you must agree to use an acceptable method of birth control for the whole study.

The following birth control measures are acceptable:

- Barrier type devices (examples are condom, diaphragm, and contraceptive sponge) used only in combination with a spermicide;
- Intrauterine device (IUD);
- Birth control pills
- Depo-provera (medroxyprogesterone acetate);
- Levonorgestrel implants;

Abstention, the rhythm method, and/or contraception by the partner are not acceptable methods of contraception.

If you do become pregnant during this study or think that you might be pregnant, you must inform your study doctor immediately. If this happens, the study doctor will discuss with you what you should do. If you get pregnant, you will be asked to stop taking part in the study and you will be asked for information about the pregnancy and the baby.

Risks from taking a blood sample

You will have routine blood samples taken from a vein in your arm by a needle stick. Risks associated with drawing blood from your arm include slight discomfort and/or bruising. Infection, bleeding, clotting, or fainting are also possible, although unlikely. The number of times that you will have a blood sample drawn for this study totals about 13 times over approximately 10 months. Each time your blood is drawn roughly 1 to 2 tablespoons of blood will be taken.

Risks from EKG

In rare circumstances, a rash or irritation at the location of the electrocardiogram electrode placement can occur due to the adhesive. If this should occur it will be assessed and treated using clinical standards of care with appropriate medication(s) and/or compresses.

Unknown risks

In addition to the risks already described, there may be other discomforts or risks from this study drug and/or procedures that we do not know about. You will be watched for signs and symptoms of any side effects and you should tell your doctor if you do not feel well or experience any unusual symptoms.

Are there benefits to taking part in this research study?
There may be no direct benefit to you by participating in this study.

Knowledge from this study may help us better understand how to treat people with ALS.

What if new information becomes available?
If additional data regarding potential safety risks become available during the study, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form which will explain the new information clearly.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

Will I need to pay for the tests and procedures?
Participation in this study will be of no cost to you. All medical exams, urine and blood tests, and study evaluations and procedures that are required for this research study are provided to you at no cost to you. You will also not need to pay for the VM202 injections. VM BioPharma Co., Ltd. pays for this research. However, if taking part in this study leads to procedures or care not included in this study, it may lead to added costs for you or your insurance company.

What happens if I am injured because I took part in this research study?
In the event of an injury resulting from your participation in this study, you will be provided with appropriate medical care. However the costs incurred may, ultimately, be borne by your medical insurance. Further information concerning this and your rights as a research subject can be obtained from Dr. John A. Kessler, M.D. or by phone [INSERT PHONE NUMBER] or by mail [INSERT MAILING ADDRESS].

What are my rights if I take part in this research study?
You have the right to refuse to sign this consent. Taking part in this research study does not take away any other rights or benefits you might have if you did not take part in the study. Taking part in this study does not give you any special privileges. You will not be penalized in any way if you decide not to take part or if you stop after you start the study. Specifically, you do not have to be in this study to receive or continue to receive medical care from your doctor. If you stop the study you would still receive medical care for your condition although you would not be able to get the VM202 product.

For any questions pertaining to your rights as a research subject, you may contact [PROVIDE CONTACT NAME] of the Institutional Review Board [PROVIDE NAME OF IRB AND CONTACT PHONE NUMBER].

What about confidentiality?

The personal information obtained about you during the course of this study will remain confidential. When recording the results of the study you will be referred to only by a unique subject identifier code number and your initials. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records.

Your records may be reviewed in order to meet Federal Food and Drug Administration (US FDA) regulations, or other national and/or local health regulatory authorities. Your records may be copied by, or for these groups. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Copies of the study records that do not include your name, but may be traced back to you may also be given to the groups listed below. The Sponsor may send a copy of the records to the FDA or other regulatory agencies.

By agreeing to participate in this research study, you consent to give representatives of the following entities access to your research-related medical records to ensure the proper conduct of the research and verify the accuracy of the collected data. Clinical monitors, auditors, IRB members, and regulatory authorities will be granted access to your original medical records for verification of clinical trial procedures and/or data, without violating your confidentiality, to the extent permitted by the applicable laws and regulations.

Reviewers for the study may include the Sponsor (VM BioPharma Co., Ltd.), or its representatives such as members of the Steering Committee, Executive Committee or Data Monitoring Committee, the Contract Research Organization identified as MedTech Consultants, Inc., and the IRB or other Research Committee(s) that approve and oversee research in the hospitals and clinics. Additionally, representatives of national regulatory authorities (for example the Food and Drug Administration in the USA), representatives of the central laboratory facilities appointed by the Sponsor responsible for analyzing the urine and blood tests, and other representatives as designated by the Sponsor who will have a role in the handling and analysis of the study data or in trial operations.

Complete confidentiality cannot be promised because information needs to be shared as described. However, information will be collected and shared following professional standards of confidentiality.

What will happen to the results of this study?

The results of this research study will be used to support an application to regulatory agencies that approve drugs for use on prescription. In addition, the results may be used in scientific publications or presented at medical meetings. Your identity as a participant will not be revealed.

Who has reviewed this study?
The study has been reviewed by the FDA, and an IRB (research ethics committee).

Who can answer my questions?
You may talk to the study doctor or IRB at any time about any questions or concerns you have on this study. A copy of this form will be placed in your medical record. A copy of this form will also be given to you.

What alternatives are there to participation in this study?
Riluzole (Rilutek®) is an available medication that has been shown to lengthen survival time in ALS patients, and you will be able to continue taking riluzole if you were taking this medication at the time of study entry. Currently, however, there are no approved drugs or treatment strategies known to stop or reverse the progression of ALS.

STATEMENT OF CONSENT

I confirm that I have read and understand this consent form. I confirm that the purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have decided of my own free will to agree to take part in this study.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

I understand that sections of any or all of my medical records may be reviewed by representatives of the Sponsor, VM BioPharma, its representatives, or by regulatory authorities. I give permission for these individuals to have access to my records. I understand that I will not identified by name in any report concerning the study. I understand that a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify me. I understand that I will be provided clinically appropriate medical care and that I have access to my doctor in case of any injury or deterioration in my health or well-being caused directly by my participation in this study.

(Printed Name of Participating Subject)		
(Signature of Participating Subject)	Date	: Time
(Printed Name of Physician or his/her Representative Obtaining Consent		
(Signature of Physician or his/her Representative Obtaining Consent)	Date	: Time

Original copy for researcher/site file; 1 copy for subject.

Appendix 3. Medications Excluded from Use During the Study

WASHOUT TABLE FOR COX-2 INHIBITORS & STEROIDS

Drug	Example of Common Name(s)	Minimum Dose Allowed During Study	Washout Period
Cox-2 specific Inhibitors			
celecoxib	Celebrex	none	2 weeks
Non-steroidal Anti-inflammatory Drugs (NSAIDs: nonspecific inhibitors of both Cox-1 and Cox-2)			
acetylsalicylic acid	Aspirin Arthritis Foundation Safety Coated Aspirin, Bayer Aspirin, Bayer Children's Aspirin, Ecotrin	81 mg daily	2 weeks for doses over 81 mg daily
diclofenac	Voltaren Arthrotec, cambia, cataflam, flector, pennsaid, solaraze, zipsor	none	2 weeks
diflunisal	Dolobid	none	2 weeks
etodolac	Lodine	none	1 week
fenoprofen	Nalfon	none	1 week
flurbiprofen	Ansaid	none	1 week
ibuprofen	Motrin, Advil, caldorol, profen	none	1 week
idomethacin	Indocin	none	1 week
ketoprofen	Nexcede, Orudis	none	None for topical formulation, 1 week for all others
ketorolac	Sprix, acuvail, acular	none	1 week
mefenamic acid	Ponstel	none	1 week
meloxicam	Mobic	none	1 week
nabumetone	Relafen, Relifex and Gambaran	none	1 week
naproxen sodium	Aleve, Anaprox, Antalgin, Feminax Ultra, Flanax, Inza, Midol Extended Relief, Miranax, Naposin, Naprelan, Naprogesic, Naprosyn, Narocin, Proxen, Synflex, Xenobid	none	2 weeks
oxaprozin	Daypro	none	1 week
piroxicam	Feldene	none	1 week
sulindac	Clinoril	none	1 week
tolmetin	Tolectin	none	1 week
Corticosteroids (topical, injected, oral)	Prednisone, betamethasone, dexamethasone, cortisone, triamcinolone	none†	1 week

Please note, some of these medications are provided in combination with other drugs in new formulations (*e.g.* AGGRENOX® (aspirin/extended-release dipyridamole); Excedrin (acetaminophen; aspirin; caffeine))
† inhaled steroids for the treatment of respiratory disorders are allowed

Appendix 4. Test Article Administration

1. ***Test article preparation***

VM202 - VM202 is supplied in a sterile glass vial containing 2.5 mg of lyophilized study product. Before administration, it will be reconstituted with 5.0 mL of water for injection (WFI) for a final VM202 concentration of 0.5 mg / mL. Each reconstituted vial is only to be used for one subject.

ALS patients will receive injections both in the upper limbs and lower limbs. In order to reduce the injection burden on the ALS patient, injection of the upper limbs will be performed on separate visits from injection of the lower limbs. Depending on whether the upper or lower limbs will be injected first VM202 will be prepared as follows:

Table 5. Single dose preparation and delivery for Day 0, Day 7, Day 14, and Day 21 Visits

Treatment Arm	Number of Vials Reconstituted at each visit	Number of injections†	Total Volume to be Injected
Upper Limb Injections 13 mg VM202	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

†Injection volume for each individual injection = 0.5 mL

2. ***Test material administration*** – Patients will receive injections of VM202 on Day 0, Day 7, Day 14 and Day 21. A fine needle (*e.g.* 27 gauge, 1") suitable for IM injections will be used. Distribute injection sites evenly over each target muscle group, carefully avoiding fascia.

- Inject the entire amount of the drug per each injection in about 3-5 seconds. Immediately after completion of injection, lightly press the injection site with the finger head in order to prevent reflux. Do not massage the injection site.

- Subsequent administrations – Subsequent administrations should also be distributed evenly over each target muscle, and, as much as is possible, at different injection sites (if previously identified by an indelible marker). If marks made to identify previous injection sites are visible, every effort should be made to inject at alternate locations.

Sample injection sites for upper limb injections and lower limb injections are depicted in Figure 4 and Figure 5, respectively. The first eligible subject will begin with the lower limb injection series as assigned by the Sponsor or its designee and will be injected in accordance with the schedule outlined in Table 6.

Table 6. Group 1 Injection Schedule

TARGET AREA	DOSE VM202 (mg) / TARGET MUSCLE, (NUMBER OF INJECTIONS / MUSCLE GROUP / SIDE (R/L))				TOTAL DOSE (TOTAL NUMBER OF INJECTIONS (R +L))
	DAY 0	DAY 7	DAY 14	DAY 21	
[redacted]					
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]					
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]					
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The next sequentially eligible patient will begin with injection of the upper limbs as assigned by the Sponsor or its designee (see Table 7). Subsequent eligible patients will be treated in an alternating fashion as assigned by the Sponsor or its designee, such that 9 patients will have initiated their VM202 injections in the lower limbs and 9 patients will have initiated their VM202 injections in the upper limbs. ***Please note: Regardless of injection order, all subjects will receive the same final dose of VM202 and the same number of injections per muscle group.***

Table 7. Group 2 Injection Schedule

TARGET AREA	DOSE VM202 (mg) / TARGET MUSCLE, (NUMBER OF INJECTIONS / MUSCLE GROUP / SIDE (R/L))				TOTAL DOSE (TOTAL NUMBER OF INJECTIONS (R + L))
	DAY 0	DAY 7	DAY 14	DAY 21	
[redacted]					
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]					
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]					
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]					
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 5. Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)

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

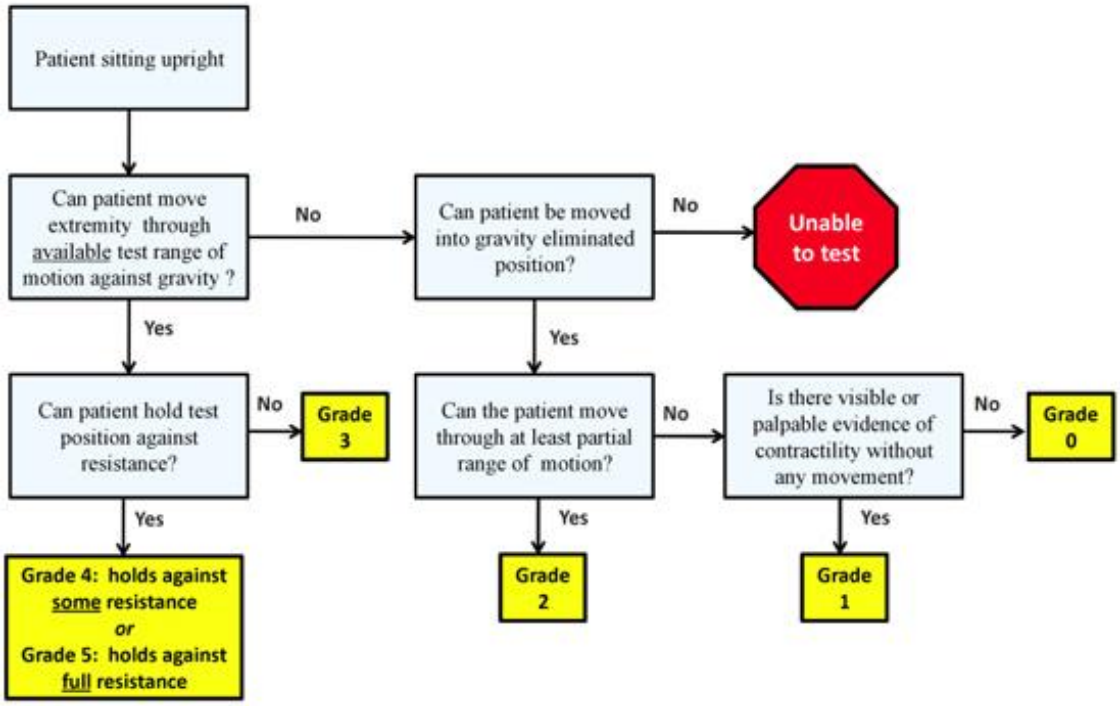
Appendix 6. Medical Research Council (MRC) Scale for Muscle Strength Testing

The following muscle groups will be evaluated using the MRC Scale:

Muscle Group	MRC Scale Score					
	0	1	2	3	4	5
Right upper arm abduction						
Left upper arm abduction						
Right elbow flexion						
Left elbow flexion						
Right wrist extension						
Left wrist extension						
Right wrist flexion						
Left wrist flexion						
Right index finger abduction						
Left index finger abduction						
Right thumb abduction						
Left thumb abduction						
Right knee extension						
Left knee extension						
Right foot dorsal flexion						
Left foot dorsal flexion						
Right foot plantar flexion						
Left foot plantar flexion						
Total score (90)						

0 - No contraction
1 - Flicker or trace contraction
2 - Active movement, with gravity eliminated
3 - Active movement against gravity
4 - Active movement against gravity and resistance
5 - Normal power

Evaluation will proceed using the following algorithm:



General Guidelines

1. For each muscle tested, the examiner stands to the side being tested, and the subject is sitting upright and positioned to allow full movement of the joint against gravity.
2. The examiner demonstrates the desired movement against gravity. The examiner then requests the subject to repeat the motion.
3. If the subject can move through the desired range of motion against gravity, the examiner attempts to apply resistance in the testing position while stating "*Hold it, don't let me push it down" or "Hold it, don't let me bend it*"
4. If the subject tolerates no resistance, the muscle score is Grade 3. If the subject tolerates some resistance, the score is Grade 4, and full resistance, Grade 5.
5. If the subject cannot move against gravity, the subject is repositioned to allow movement of the extremity with gravity eliminated. If supporting the limb, the examiner provides neither assistance nor resistance to the subject's voluntary movement. This gravity-eliminated positioning will vary for each muscle tested. If the subject cannot complete at least partial range of motion with gravity eliminated, the muscle or tendon is observed and/or palpated for contraction.
6. For a bedridden subject who cannot sit up in a bed placed in the chair position or on the edge of the bed, alternate positions for testing the lower extremity are included in this protocol.

Upper Arm (shoulder) Abduction

- Testing position - arm out from the side at shoulder level
- The examiner demonstrates the motion, then states "*Lift your arm out to the side to shoulder level.*" The hand giving resistance is contoured over the subject's arm just above the elbow. The other hand stabilizes the shoulder above the shoulder joint. The examiner states "*Hold it,*

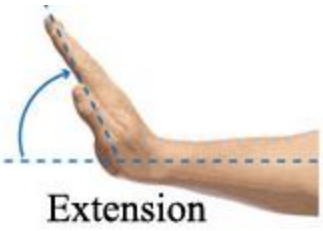
don't let me push it down." To assess grades 3, 4, or 5, please see General Guidelines, section 4 above.

- If weaker than Grade 3, the subject lies supine with arms at the side. The examiner supports the arm just above the elbow and at the wrist to assure that the shoulder does not externally rotate (turn outward). The subject attempts to move the arm out to the side. The examiner states: "*Try to move your arm out to the side*". Grade 2 is assigned if the subject moves with gravity eliminated.
- If weaker than Grade 2, the examiner states "*Try to move your arm out to the side*" and palpates the middle deltoid muscle for contraction, and scores as Grade 1 or 0 as previously defined.

Elbow Flexion

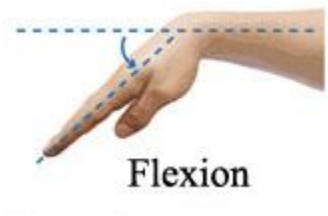
- Test position - forearm supinated and flexed slightly more than 90 degrees.
- Verbal instructions: "*Bend your elbow slightly more than 90 degrees*". The hand giving resistance is contoured over the flexor surface of the forearm proximal to the wrist. The examiner's other hand applies counterforce by cupping the palm over the anterior superior aspect of the shoulder. The examiner then states: "*Hold it. Don't let me push it down*" and scores Grades 3, 4, or 5 as previously described.
- If weaker than Grade 3, the shoulder is abducted to 90 degrees. The examiner supports the arm under the elbow and, if necessary, the wrist as well. The forearm is turned with the thumb facing the ceiling. With the elbow extended, the subject attempts to flex the elbow. The examiner states: "*Try to bend your elbow.*" Grade 2 is assigned if the subject can flex the elbow.
- If weaker than Grade 2, the forearm is supinated and positioned at the side in approximately 45 degrees of elbow flexion. The examiner states "*Try to bend your elbow*", palpates the biceps tendon and scores as either Grade 1 or 0.

Wrist Extension



- Test position - arm at the side, elbow flexed to 90 degrees with the forearm pronated and the wrist fully extended.
- Verbal instructions: "*Bend your wrist up as far as possible.*" The examiner's hand giving resistance is placed over the back of the subject's hand just distal to the wrist. The examiner's other hand supports the subject's forearm. The examiner then states: "*Hold it. Don't let me push it down*" and scores Grades 3, 4 or 5.
- If weaker than Grade 3, the elbow is flexed to 90 degrees and forearm turned with thumb facing the ceiling. The forearm and wrist are supported by the examiner. The examiner states: "*Bend your hand toward me*". Grade 2 is assigned if the subject can extend the wrist.
- If weaker than Grade 2, the examiner states "*Bend your wrist toward me*" and palpates the two extensor tendons, one on each side of the wrist and scores as Grade 1 or 0. The examiner is careful not to palpate the tendons in the middle of the wrist.

Wrist Flexion



- Test position - arm at the side, elbow flexed to 90 degrees with the forearm supinated and the wrist fully extended.
- Verbal instructions: "*Bend your wrist up as far as possible.*" The examiner's hand giving resistance is placed on the palm of the subject's hand just distal to the wrist. The examiner's other hand supports the subject's forearm. The examiner then states: "*Hold it. Don't let me push it down*" and scores Grades 3, 4 or 5.
- If weaker than Grade 3, the forearm and wrist are supported by the examiner. The examiner states: "*Bend your hand toward me*". Grade 2 is assigned if the subject can flex the wrist.
- If weaker than Grade 2, the examiner states "*Bend your wrist toward me*" and palpates the flexor tendons and scores as Grade 1 or 0.
-

Index finger abduction

- Test position - arm at the side, elbow flexed to 90 degrees, fingers extended, with the wrist in the midposition between supination and pronation.
- Verbal instructions: "*Spread your fingers apart.*" The examiner's finger giving resistance to the superior portion of the tip of the index finger. The examiner then states: "*Hold it. Don't let me push it down*" and scores Grades 3, 4 or 5.
- If weaker than Grade 3, the forearm and wrist are pronated and the hand is placed on a flat surface. The examiner states: "*Spread your fingers apart*". Grade 2 is assigned if the subject can abduct the index finger.
- If weaker than Grade 2, the examiner states "*Spread your fingers apart*" and palpates the FDI muscle belly and scores as Grade 1 or 0.

Thumb abduction

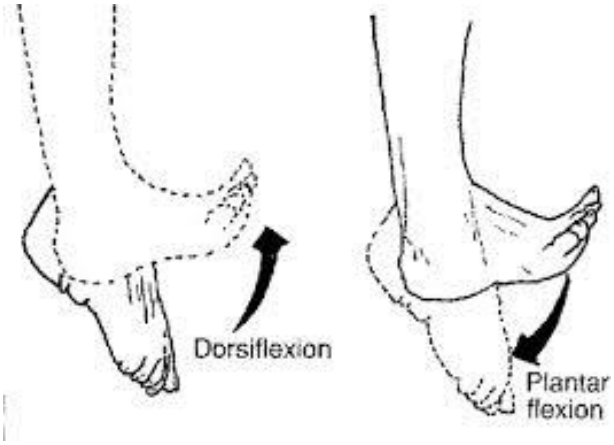
- Test position - arm at the side, elbow flexed to 90 degrees, forearm supinated and supported on a flat surface, with the wrist and fingers extended.
- Verbal instructions: "*Raise your thumb straight up*" such that the thumb moves in a plane that is at a right angle to the palmar surface. The examiner's finger gives resistance to the superior portion of the thumb. The examiner then states: "*Hold it. Don't let me push it down*" and scores Grades 3, 4 or 5.
- If weaker than Grade 3, the forearm and wrist are placed in midposition between supination and pronation. The examiner then states: "*Move your thumb inward*" such that the thumb moves in a plane that is at a right angle to the palmar surface. Grade 2 is assigned if the subject can abduct the thumb.
- If weaker than Grade 2, the examiner states "*Move your thumb inward*" and palpates the APB muscle belly and scores as Grade 1 or 0.

Knee Extension

- Test position - sitting upright with the knee fully extended to 0 degrees. Avoid knee hyperextension.
- Verbal instructions; "*Straighten your knee*". The hand giving resistance is contoured on top of the leg just proximal to the ankle. The other hand is placed under the thigh above the knee. The examiner then states "*Hold it. Don't let me bend it*" and scores Grades 3, 4 or 5.
- If weaker than Grade 3, the subject lays on the non-testing side. The examiner stands behind the subject at knee level. The leg not being tested may be flexed for stability. One arm cradles the leg being tested around the thigh with the hand supporting the underside of the knee. The other hand holds the leg just above the ankle. The examiner states: "*Straighten your knee.*" Grade 2 is assigned if the subject can extend the knee (Figure 3).
- If weaker than Grade 2, the subject is supine and the examiner states: "*Push the back of your knee down*" or "*Tighten your knee cap*" and palpates the quadriceps tendon, and scores as Grade 1 or 0.

Foot Dorsiflexion

- Test position - sitting, with the heel on floor, foot in full dorsiflexion, and shoes and socks removed.
- Verbal instructions: "*Bend your foot up as far as possible.*" The toes are relaxed during the test. The hand giving resistance is cupped over the top of the foot proximal to the toes. The other hand is contoured around the front of the leg just proximal to the ankle. The examiner then states "*Hold it, don't let me push it down*" and scores Grade 3, 4 or 5.
- If weaker than Grade 3, but there is partial range of motion against gravity, assign Grade 2.
- If weaker than Grade 2, palpate the tibialis anterior tendon, and score as Grade 1or 0.
- The bedridden subject is tested supine, with the leg extended and a pillow placed under the knee.



Foot Plantarflexion

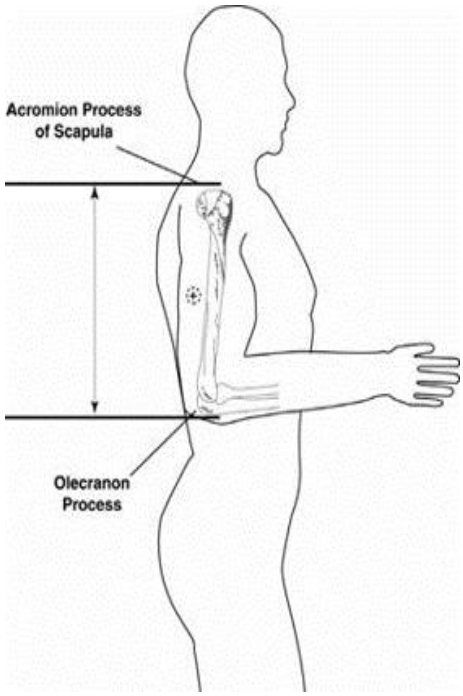
- Test position - sitting, with the heel on floor, foot in full dorsiflexion, and shoes and socks removed.
- Verbal instructions: "*Lift your heel and point your toes down as far as possible.*" The hand giving resistance is cupped over the top of the foot proximal to the ankle. The other hand is contoured around the front of the leg just proximal to the ankle. The examiner then states "*Hold it, don't let me push it down*" and scores Grade 3, 4 or 5.
- If weaker than Grade 3, but there is partial range of motion against gravity, assign Grade 2.
- If weaker than Grade 2, palpate the tibialis anterior tendon, and score as Grade 1or 0.
- The bedridden subject is tested supine, with the leg extended and a pillow placed under the knee.

Appendix 7. Measuring Muscle Circumference

To reduce variability, whenever possible, the same health care professional should conduct all of the muscle circumference measurements. ***Conduct all measurements bilaterally.***

Mid-upper Arm Muscle Circumference:
Locate the midpoint of the upper arm.

- Seat the subject in a comfortable chair with his/her hip and knee joint flexed at 90° and their forearm resting on a supporting armrest with the palm facing up.
- The elbow should be flexed at 90 degrees with palm facing upwards
- Stand **behind** the subject & locate the **lateral tip of the acromion** and the most **distal point on the olecranon** process
- Place a tape measure so that it passes between these 2 landmarks and mark the midpoint

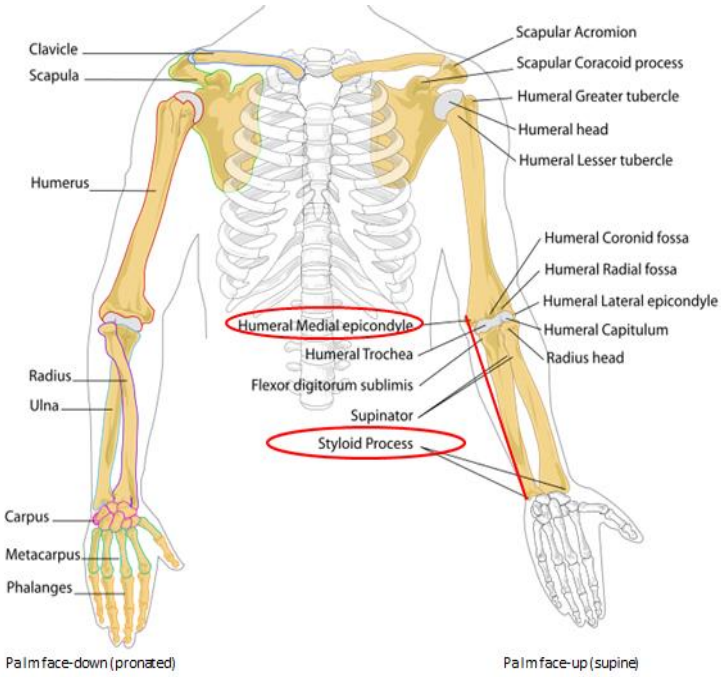


Measure the upper arm circumference

- The subject can stand with arms hanging freely at the sides or stay seated and dangle his/her arms at his/her side with the palms facing the thighs
- Place the tape measure perpendicular to the long axis of the arm at the **marked midpoint** and measure the **circumference to the nearest mm**. (*e.g.* 18.1 cm)

Forearm Muscle Circumference:

- Seat the subject in a comfortable chair with his/her hip and knee joint flexed at 90° and his/her forearm resting on a supporting armrest with the palm facing up.
- The elbow should be flexed at 120 degrees with palm facing upwards
- Mark the **proximal one third point** of a vertical line that joins the **medial epicondyle** to the **styloid process of the ulna**.

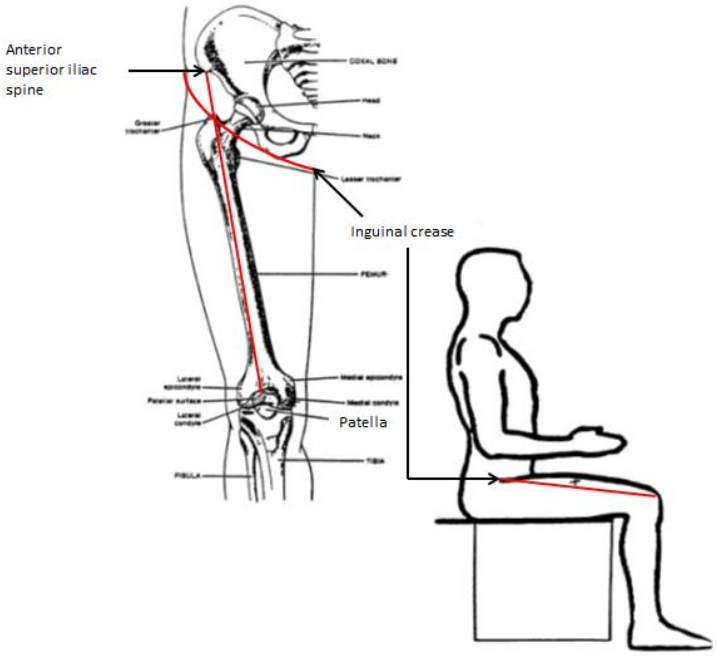


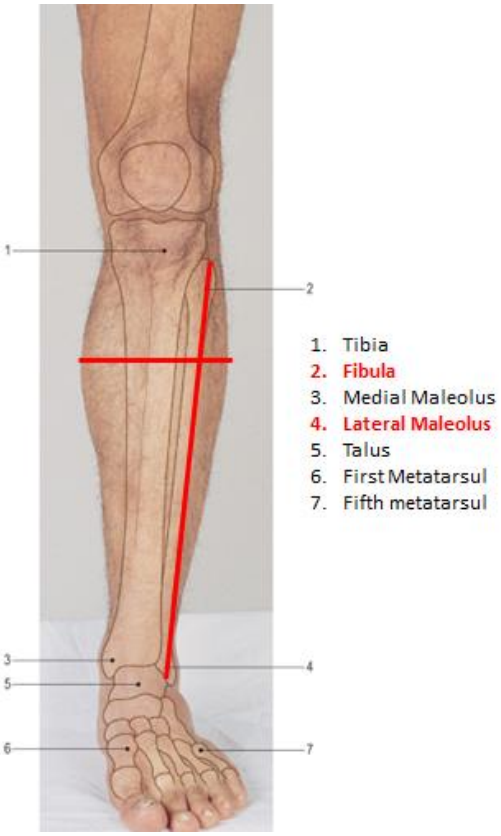
Measure the forearm circumference

- The subject can stand with arms hanging freely at the sides or stay seated and dangle his/her arms at his/her side with the palms facing the thighs
- Place the tape measure perpendicular to the long axis of the arm at the **marked point** and measure the **circumference to the nearest mm**.

Mid-thigh Muscle Circumference:

- Seat the subject in a comfortable chair with his/her hip and knee joint flexed at 90°.
- Identify the **anterior superior iliac spine** (slightly above the inguinal crease) and the **superior edge of the patella**. No pressure should be applied at the inguinal crease, but, folds of fat tissue may have to be lifted on to measure at the crease.
- Mark the midpoint of the thigh
- Place the tape measure perpendicular to the long axis of the thigh at the **marked point** and measure the **circumference to the nearest mm**.





Calf Circumference:

- Seat the subject in a comfortable chair with his/her hip and knee joint flexed at 90°.
- Identify the **fibular head** and the **lateral malleolus**.
- Mark the lower leg at the one third point of a vertical line that joins the fibular head to the lateral malleolus
- Place the tape measure perpendicular to the long axis of the lower leg at the **marked point** and measure the **circumference to the nearest mm**.

Appendix 8. Dynamometry

Finger Pinch Strength
Maximal finger pinch strength will be tested using a MicroFet 4 digital dynamometer (Hoggan Health Industries, West Jordan, Utah). Measurements should be conducted bilaterally.

- Seat the subject in a comfortable chair with his/her shoulder adducted and neutrally rotated, and with the elbow positioned at 90°, and the forearm and wrist in a neutral position.
- Demonstrate how to use the finger pinch and to show that pinching very tightly registers the best score.
- Ask the subject to hold the dynamometer between the lateral aspect of the middle phalanx of the index finger and thumb pad.

- Instruct the subject to squeeze as hard as he/she can for 3 seconds.
- Repeat 3 times. Record maximal pinch grip force for each trial.
- The average of 3 consecutive tests will be calculated for each subject.

Grip Strength
Maximal grip pinch strength will be tested using a MicroFet 4 digital dynamometer (Hoggan Health Industries, West Jordan, Utah). Measurements should be conducted bilaterally.

- Seat the subject in a comfortable chair with his/her shoulder adducted and neutrally rotated, and with the elbow positioned at 90°, and the forearm with the wrist just over the end of the arm of the chair—wrist in a neutral position, thumb facing upwards.
- Demonstrate how to use the handgrip dynamometer to show that gripping very tightly registers the best score.
- Position the subject‘s hand so that the thumb is around one side of the handle and the four fingers are around the other side. The instrument should feel comfortable in the hand. Alter the position of the handle if necessary.
- The observer should hold the head of the dynamometer as the subject grips it. The aim of this is to support the weight of the dynamometer

(to negate the effect of gravity on peak strength), but care should be taken not to restrict its movement.

- Instruct the subject to squeeze as hard as he/she can for 3 seconds.
- Repeat 3 times. Record maximal grip force for each trial.
- The average of 3 consecutive tests will be calculated for each subject.

Lower Leg Extension

Maximal lower leg extension strength will be tested using a MicroFet 3 digital dynamometer (Hoggan Health Industries, West Jordan, Utah). Measurements should be conducted bilaterally.

- Seat the subject in a comfortable chair with his/her hip and knee joint flexed at 90° and feet flat on the floor.
- The examiner places the dynamometer against the anterior leg proximal to the malleoli.
- Instruct the subject to straighten out his/her knee and hold his/her leg in that position for 3 seconds.
- Repeat 3 times.
- Record maximal leg extension for each trial
- The average of 3 consecutive tests will be calculated for each subject.