Motric Bio
Restoring movement

CLINICAL STUDY PROTOCOL

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human, Single and Multiple Ascending Dose Study of MTR-601 in Healthy Volunteers
Study Number:	MTR-601-NHV-101
Study Drug:	MTR-601
Brief Title:	Single and Multiple Ascending Dose Study of MTR-601 in Healthy Individuals
Phase of Development:	1
Sponsor Name:	Motric Bio 1111 Broadway, Suite 300 Oakland, CA
Medical Monitor:	Dan Meyers, MD [redacted]
Regulatory Agency Identifier Number(s):	IND 165262
Issue Date:	15 April 2024 v4.0 Amendment 3.0

This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines, and applicable regulatory requirements.

Confidentiality Statement

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CK-MB	creatinine kinase heart
CK-MM	creatinine kinase skeletal muscle
CrCl	creatinine clearance
CRU	clinical research unit
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	percent coefficient of variation
CYP	cytochrome P450
DRF	dose-range-finding
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FEV_1	forced expiratory volume in one second
FIH	first-in-human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

Abbreviation	Term
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	International Normalized Ratio
IP	investigational product
I-PSS	International Prostate Symptom Score
IRB	Institutional Review Board
IUD	intrauterine device
LE	lower extremity
LVEF	left ventricular ejection fraction
MAD	multiple ascending dose
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
NOS	*nil per os,* nothing by mouth
PI	principal investigator
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
QD	once daily
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
SRC	Safety Review Committee
STD	standard deviation
TEAE	treatment-emergent adverse events
UE	upper extremity

Abbreviation	Term
ULN	upper limit of normal
WBC	white blood cell

1. PROTOCOL SUMMARY

1.1. Synopsis

<table>
<tr><td>Sponsor:</td><td colspan="5">Motric Bio</td></tr>
<tr><td>Study Title:</td><td colspan="5">A Randomized, Double-Blind, Placebo-Controlled, First-in-Human, Single and Multiple Ascending Dose Study of MTR-601 in Healthy Volunteers</td></tr>
<tr><td>Brief Title:</td><td colspan="5">Single and Multiple Ascending Dose Study of MTR-601 in Healthy Volunteers</td></tr>
<tr><td>Protocol Number:</td><td>MTR-601-NHV-101</td><td>Phase:</td><td>1</td><td>Study Center:</td><td>Phase 1 – Clinical Research Unit, USA</td></tr>
<tr><td>Investigational Product:</td><td colspan="5">MTR-601 capsules are supplied containing 5 mg or 20 mg of MTR-601 MTR-601 placebo capsules are supplied to match MTR-601 capsules</td></tr>
<tr><td>Dosage Forms and Route of Administration:</td><td colspan="5">MTR-601 is an orange opaque capsule for oral administration, dosed once daily.</td></tr>
<tr><td rowspan="5">Objectives and Endpoints:</td><td colspan="3">Objectives</td><td colspan="2">Endpoints</td></tr>
<tr><td colspan="5">Primary</td></tr>
<tr><td colspan="3">To assess the safety and tolerability of single and multiple doses of MTR-601 in normal healthy volunteers under fed and fasted conditions.</td><td colspan="2">The primary endpoint is safety assessed after single and multiple dose administration by:
• Incidence, severity, and relatedness of adverse events (AEs; number and incidence of treatment-emergent adverse events [TEAEs])
• Incidence of laboratory abnormalities, based on hematology, clinical chemistry, coagulation, urinalysis test results
• Vital sign measurements
• 12-lead electrocardiograms (ECGs)
• Echocardiography
• Physical and neurological examinations
• Telemetry and oximetry
• Spirometry
• Urinary System Ultrasonography</td></tr>
<tr><td colspan="5">Secondary</td></tr>
<tr><td colspan="3">To evaluate the plasma and urine pharmacokinetics (PK) of MTR-601
[redacted]</td><td colspan="2">Pharmacokinetic evaluations may include:
• Concentration-time relationships
• Estimations of dose proportionality at steady state
• Estimation of time to achieve steady state
• Potential MTR-601 metabolites
[redacted]</td></tr>
</table>

	Muscle accumulation of MTR-601 by muscle biopsy and other potential mechanistic, predictive and PD markers of MTR-601	[redacted] • An evaluation of concentration-effect relationships with other parameters (e.g., cytochrome P450 isoenzymes that affect absorption, distribution, metabolism, and excretion [ADME], other muscle parameters, gender, etc.) that may be performed at a later date and described in a stand-alone analysis plan and report • Muscle accumulation assessed by muscle biopsy and estimates of body muscle mass • An evaluation of potential MTR-601 PD and/or predictive biomarkers may be conducted (genetic and/or protein endpoints)
Study Design:	This randomized, placebo-controlled, first-in-human (FIH) study of MTR-601 in normal healthy volunteers will consist of 5 single ascending dose (SAD) level cohorts (including 1 SAD Level 2, Two-Dose cohort), and up to 6 multiple ascending dose (MAD) level cohorts, each comprised of 8 subjects (6 MTR-601; 2 placebo). The total sample size will be up to 88 subjects to accommodate withdrawal of consent or replacement for other non-treatment-emergent adverse events (non-TEAE) reasons.	

SAD/MAD Cohort [a,b]	Dose [g]	Fasted	Fed Standard [c]	N [e]
SAD Level 1	10 mg		✓	8 [f]
SAD Level 2, Two-Dose [d]	20 mg	✓	✓	8 [f]
SAD Level 3	40 mg		✓	8 [f]
SAD Level 4 (Optional)	80 mg		✓	8 [f]
SAD Level 5	160 mg		✓	8
MAD Level 1	10 mg		✓	8
MAD Level 2	20 mg		✓	8
MAD Level 3	20 mg		✓	8
MAD Level 4	40 mg		✓	8
MAD Level 5	80 mg		✓	8
MAD Level 6	≤160 mg		✓	8

Abbreviations: MAD = multiple ascending dose; N = number of subjects; SAD = single ascending dose.
Fasted: Subjects will remain NPO (nothing by mouth -clear liquids allowed) for at least 8 hours prior to dosing.
a. Subjects will participate in only 1 dose level cohort in either the SAD; SAD Level 2 Two-Dose or MAD portions of the study.

b. All subjects regardless of cohort, will have doses administered with staggered timing such that no subjects shall be dosed simultaneously.
c. Subjects will be fed a standard (not high-fat) breakfast 30 minutes before dosing.
d. Subjects in the SAD Level 2, Two-Dose level cohort: For the first dose, subjects will be fasting; for the second dose, subjects will be fed a not high-fat breakfast 30 minutes before dosing.
e. 6 MTR-601 and 2 placebo per cohort. SAD cohorts will be randomized 1:1 for sentinels and 5:1 for the remaining subjects, while MAD cohorts will be randomized 6:2.
f. All SAD dose cohorts (including Level 2, Two-Dose) will have 2 sentinel subjects followed at least 72 hours later by the remaining 6 subjects.
g. Cohort dose may be modified by the Sponsor based upon pharmacokinetic and safety results from earlier cohorts.

SAD Levels 1–5 dosing:

- Each of the SAD dose level cohorts will have 2 sentinel subjects followed at least 72 hours later by the remaining 6 subjects in 1 or more groups in a staggered fashion. Both sentinel subjects will be evaluated for 72 hours by the Investigator for safety prior to dosing the cohort's remaining 6 subjects.
- Dosing will begin at dose Level 1 (10 mg).
- Subjects in SAD Levels 1,3, 4 and 5 will be dosed in a fed state (standard non-high-fat breakfast).
- Subjects in the SAD Level 2, Two-Dose (20 mg) will be dosed in a fasting state on Day 1 with a subsequent 4-day washout period, followed by dosing in a fed state (standard not- high fat breakfast) on Day 6.
- SAD Level 4 (80 mg) dosing is optional and may be adjusted based upon PK and safety results from earlier cohorts.

MAD Levels 1–6 dosing:

- The MAD portion of the study will commence at MAD Level 1 (10 mg) after the safe completion of the subjects in at least the SAD Level 2 Two-Dose cohort.
- Subjects in MAD Levels 1–6 will be dosed in a fed state (standard non-high-fat breakfast) over 14 continuous days of dosing.
- MAD cohorts may be enrolled in small groups to accommodate clinic scheduling, with subjects dosed in a staggered fashion.

Dose Escalation:

The study will be monitored by a Safety Review Committee (SRC) comprised of the Principal Investigator (PI), the Medical Monitor, and the Sponsor. The SRC is intended to ensure treatment does not pose undue risk to subjects. Dose escalation to the next higher dose level cohort will not take place until the SRC has assessed the data through discharge (supplemental plasma PK information on a previously treated cohort may be requested as a part of the review) and determined that adequate safety and tolerability has been demonstrated to permit proceeding.

The planned dose levels for MAD Cohort 5 (80 mg) and Cohort 6 (160 mg) may be decreased based on the plasma PK from the preceding MAD cohort. Escalation will proceed no higher than a dose that is estimated to yield ≤ ½ of the rat 28-day NOAEL exposure (C_{max} ≤ 421 ng/mL, AUC_{0-24} ≤ 6,600 ng*hr/mL).

The SRC may recommend:

- Ascending to the planned next higher dose level
- Ascending to a dose level lower than the planned next higher dosage level cohort
- Repeat dosing at the current dose level

- Descending to an intermediate dose above a previously tolerated dose level
- Pausing dose escalation
- Stopping the study

Dose Escalation Criteria:
Participation in the clinical study may be discontinued by an Investigator (or delegate) in charge of the study or by the Sponsor for any of the following reasons in the table below:

Stopping Rules:

Stopping Rules[d]	**Individual Subject Stopping Rules[a]**	**Cohort and/or Dose Escalation Stopping Rules**
ALT or AST ≥3 × ULN	≥1 subject	N/A
ALT or AST >5 × ULN	N/A	≥2 subjects
Creatinine >1.2 × ULN or an increase in serum creatinine by ≥30 µmol/L within 24 hours or an increase in serum creatinine to ≥1.5 × baseline within 7 days	≥1 subject	≥2 subjects
QTcB and QTcF >500 msec or change from baseline: QTc >60 msec	≥1 subject	≥2 subjects
Sustained heart rate <45 bpm or heart rate >130 bpm [b] confirmed by repeat after 30 minutes	≥1 subject	≥2 subjects
Sustained systolic blood pressure <80 or systolic blood pressure >155 mmHg confirmed by repeat after 30 minutes	≥1 subject	≥2 subjects
Sustained diastolic blood pressure >100 mmHg confirmed by repeat after 30 minutes	≥1 subject	≥2 subjects
Occurrence of a serious adverse event (SAE) in a participant not receiving placebo	≥1 subject	≥1 subject
Severe AEs in the same cohort	N/A	≥1 subject
Clinically significant laboratory abnormalities of the same character	N/A	≥2 subjects
Confirmed lower urinary tract obstruction[c]: (Two successive post-void residual volume determinations within 24 hours exceeding 100 mL) or evidence of hydronephrosis upon Ultrasound evaluation.	≥1 subject	≥1 subjects
A drop in the eGFR below 70 mL/min/1.73 m^2 (CKD-EPI) or a reduction of 25% from baseline.	≥1 subject	≥2 subjects

A confirmed[e] reduction in the FVC (forced vital capacity) done in triplicate to less than 80% of the predicted vital capacity based on gender, height and age with good expiratory effort as assessed by the Investigator	≥1 subject	≥2 subjects
Any subject who develops gross or microscopic (>5 RBC/HPF) hematuria, unless clearly caused by menses	≥1 subject	≥2 subjects
Any subject who has signs, symptoms, and urinalysis/dipstick evidence of a clinically significant urinary tract infection	≥1 subject	≥2 subjects

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bpm = beats per minute; mmHg = millimeters of mercury; msec = millisecond; N/A = not applicable; QTcB= QT correct with Bazett formula; QTcF = QT interval corrected for heart rate using Fridericia's formula; ULN = upper limit of normal.

a. When an out-of- range value meeting the stopping criteria is confirmed by a repeat assessment, the principal investigator shall institute any necessary medical or surgical intervention based on his/her clinical judgement and the standard of care for such a condition to ensure the safety of the trial participant. Such intervention may be implemented within the Clinical Research Unit or upon transfer to a local emergency room/hospital as clinically warranted.
b . When resting heart rate is between 60–100 beats per minute, use clinical judgment when characterizing bradycardia among some healthy subject populations (e.g., conditioned athletes).
c . If a lower urinary tract obstruction is suspected, a transurethral bladder catheter should be placed at the clinical research unit to confirm obstruction and remain in place if needed to manage bladder drainage.
d . Lab and eGFR values which meet stopping criteria must be confirmed with a repeat measurement.
e . FVC values meeting stopping rule should be confirmed prior to the next scheduled dose. If repeat FVC no longer meets stopping criteria, dosing may continue.

Trial Stopping Rules

The Investigator must contact the Sponsor immediately to discuss whether to suspend dosing if an AE or laboratory abnormalities indicate that continued dosing of subsequent subjects would not be tolerated or would jeopardize the subjects' safety. The Sponsor alone may suspend dosing at any time for any reason.

Clinical trial stopping rules:

- Occurrence of 1 serious adverse event (SAE) in a participant not receiving placebo
- Occurrence of 'severe' non-serious adverse reactions in a participant not receiving placebo
- Occurrence of 1 death in a participant not receiving placebo
- Occurrence of 1 case of lower urinary tract obstruction (by catheter-confirmed post void residuals) or hydronephrosis (by ultrasound).
- Occurrence of 2 or more subjects with gross hematuria (unless clearly caused by menses).
- Occurrence of 2 or more subjects with a decrease of 50% or more from baseline (Day -1) in eGFR

If any of the above scenarios occur, the study will be immediately paused. Further discussion will then occur within the SRC, and a safety review will be conducted. Following the SRC review, the study may continue if the Investigator and Sponsor agree it is safe to proceed. If the study is stopped, the maximum tolerated dose (MTD) will be declared at the dose level lower than that escalation dose.

Study Assessments and Procedures Overview:

Safety assessments will include physical and neurological examinations, vital signs, Echocardiography, Spirometry, ECG, ultrasound, IPSS (version 1-IPSS_AU1.0_eng-USori) and laboratory assessments. Adverse events will be collected from first dose through the follow-up telephone call (Day 7 for subjects in all SAD level cohorts; Day 12

for subjects in the SAD Level 2, Two-Dose cohort; Day 20 for subjects in all MAD cohorts.

Telemetry and digit oximetry will be monitored by applying at least 1 hour prior to dose administration and remain on for approximately 24 hours in the SAD cohorts. In MAD cohorts, telemetry and digit oximetry will be monitored for approximately 24 hours starting on Day 1, Day 7, and Day 14, and monitored on all dosing days from pre-dose until 12 hours post-dose for the duration of the study. Telemetry and oximetry will be interrupted to accommodate daily hygienic routines (e.g., showering).

Blood and urine sample collection for PK analysis of MTR-601 will be collected in the Clinical Research Unit (CRU) at specified time points as detailed in the Schedule of Assessments (Table 1, Table 2, and Table 3).

Spirometry measurements will include:

- Forced expiratory volume in one second (FEV_1)
- Forced vital capacity (FVC)
- FEV_1/FVC ratio (FEV_1 divided by FVC)

Dynamometry measurements will include grip strength, upper extremity (forearm extension/flexion), and lower extremity (knee extension in sitting position).

Refer to the Schedule of Assessments (Table 1, Table 2, and Table 3) for details on exact days and times of assessments.

Concomitant Therapies

Within 30 days prior to the first administration of MTR-601/placebo, subjects may not use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort.

From 14 days prior to check-in (Day -1) until the Follow-up telephone call (Day 7 for subjects in the SAD level cohorts; Day 12 for subjects in the Two-Dose level cohort; Day 20 for subjects in all MAD cohorts, are not permitted to use prescription or nonprescription medications/herbal remedies/supplements of any kind, with the exception of paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) if required for the treatment of AEs. Concomitant therapy may include urethral catheterization at the discretion of the Principal Investigator and within the current standard of care practice for urinary obstruction.

In the event concomitant medication is needed during the study to treat an AE, the medication must be recorded in the electronic case report form (eCRF)with its generic name, time of administration, dose, route, duration, and the reason for administration.

Subjects Planned and Duration:

Subjects Planned:	**Duration of IP for each subject by dose level cohort:**
Approximately 88	**SAD:** 1 day **SAD Two-Dose:** 2 days **MAD:** 14 days

Total study duration for each subject:

SAD:	A (maximum) 30-day screening period, check-in to the clinical research unit (CRU) on Day -1, a single dose of study medication on Day 1 with subsequent in-house observation of at least 96 hours [a], check-out/ discharge from the CRU, and a telephone follow-up on Day 7. The total duration will be approximately 37 days.
SAD Two-Dose:	A (maximum) 30-day screening period, check-in to CRU on Day -1, a single dose of study medication on Day 1, a 4-day washout period, a second single dose of study medication on Day 6 with subsequent in-house observation of at least 96 hours [a], check-out/discharge from the CRU, and a telephone follow-up on Day 12. The total duration will be approximately 42 days.

	MAD: A (maximum) 30-day screening period, check-in to the CRU on Day -1, daily dosing of study medication on Days 1–14 with subsequent in-house observation of at least 96 hours [a] after the last dose, check-out/ discharge from the CRU, and a telephone follow-up on Day 20. The total duration will be approximately 50 days. a. If needed (e.g., in the event of AEs), the in-house observation period may be prolonged for safety observation at the discretion of the Investigator, which will extend duration of study participation by the number of additional observation days required.
Population:	**Inclusion Criteria** Subjects who meet ALL the following inclusion criteria will be eligible to participate in the study: 1. Willing to adhere to study procedures and provide written informed consent prior to the start of any study procedures. 2. 18–45 years of age at the time of consent and in good physical health based on medical history, physical examination including vital signs, as well as laboratory, electrocardiogram (ECG), Echocardiography (LVEF in the normal range of 50-70%), normal muscle strength upon physical examination, and spirometry test values. 3. Weight ≥50 kg and body mass index (BMI) <33 kg/m^2. 4. Females or males with female partners must use a medically accepted contraceptive regimen (i.e., condoms with spermicide, abstinence, nonhormonal intrauterine device (IUD), Essure procedure, or diaphragm with spermicide) from at least 30 days prior to first dose through 90 days after the last dose OR females must be of non-childbearing potential, defined as: a. Have been surgically sterilized (e.g., bilateral oophorectomy) or hysterectomized at least 6 months prior to screening. Surgical sterilization procedures or hysterectomy must be supported with clinical documentation/medical records and noted in the Relevant Medical History/Current Medical Condition section of the electronic case report form (eCRF). b. Be postmenopausal (i.e., must have no regular menstrual bleeding for at least 2 years prior to inclusion). Menopause will be confirmed by a plasma follicle-stimulating hormone (FSH) level of >40 IU/L. 5. Non-smoker and must not have used any tobacco products within 3 months prior to screening. 6. In good physical and mental health as determined by past medical history, physical examination, psychiatric examination, 12-lead ECG, Echocardiography, spirometry, urinary system ultrasound, vital sign measurements, and clinical laboratory evaluations and calculations (e.g., eGFR greater than 90 mL/1.73 m^2) at screening or check-in to the clinical research unit (CRU) on Day -1, as assessed by the Investigator (or designee). Congenital nonhemolytic hyperbilirubinemia; or suspicion of Gilbert's syndrome based on total and direct bilirubin is not acceptable. 7. Has clinical laboratory test results within the reference ranges of the testing laboratory, except for results outside reference ranges that are deemed not clinically significant by the Investigator (or designee) at screening and check-in to the CRU on Day -1. 8. Vital signs are within normal limits after 3 minutes resting in supine position and FVC (measured in the seated position and triplicate averaged) is ≥90% of the predicted value for gender, age and height with good expiratory effort. **Exclusion Criteria** Subjects who meet any of the following exclusion criteria will be excluded from participation in the study:

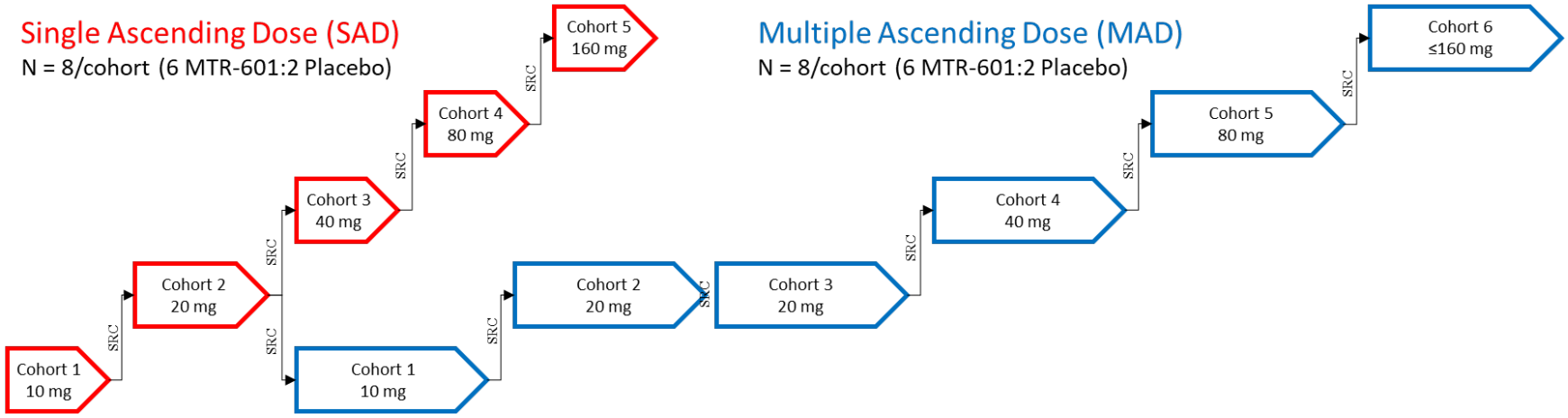
	1. History of, or physical examination findings indicating, clinically significant endocrine, neurological, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal (including any evidence of pre-existing renal disease and/or obstructive uropathy for any reason, including benign prostatic hypertrophy and kidney stones), respiratory, genitourinary, or muscle abnormalities or diseases that, in the opinion of the Investigator, would render the subject being unsuitable for the study. 2. Unwilling or unable to refrain from strenuous exercise for 3 days prior to check-in and during study or elevated total CK, CK-MB, CK isoenzymes or myoglobin at screening, or elevated total CK, CK-MB or myoglobin on Day -1. 3. Unwilling to discontinue coffee (containing caffeine) and other caffeine-containing beverages (e.g., sodas, energy drinks) for at least 72 hours before check-in and throughout the entirety of the study. 4. Use of tobacco- or nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 3 months prior to check-in to the CRU on Day -1 and throughout the entirety of the study (urine cotinine levels will be measured during screening for all subjects; subjects with cotinine values greater than 500 ng/mL will be excluded). 5. Requires prescription or nonprescription medications/herbal remedies/supplements of any kind (with the exception of paracetamol/acetaminophen 2 g/day for up to 3 consecutive days) from 14 days prior to check-in (Day -1) and throughout the entirety of the study; uses or intends to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing. 6. History or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, urinary, hematological, pulmonary, gastrointestinal, neurological, psychiatric, respiratory, or endocrine disorder, unless determined by the Investigator (or designee) and agreed by the Medical Monitor to be not clinically significant. 7. Active or history of metabolic, cardiovascular, or cerebrovascular disease, including hypertension, angina, ischemic heart disease, transient ischemic attacks, bundle branch block, evidence of myocardial ischemia, stroke, and peripheral arterial disease sufficient to cause symptoms and/or require therapy to maintain stable status. 8. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee). 9. Active neoplastic disease or history of any neoplastic disease within 5 years of screening (except for basal or squamous cell carcinoma of the skin or carcinoma in situ that has been definitively treated with standard of care). 10. Active infection (e.g., sepsis, pneumonia, abscess) or a serious infection (e.g., resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to dosing. 11. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed). 12. Any of the following at screening and/or pre-dose: a. Triplicate averaged QT interval corrected for heart rate using Fridericia's formula (QTcF), QRS duration (>120 msec), PR interval (>220 msec) outside of normal limits confirmed by repeat measurement, unless deemed non-clinically significant by PI and agreed by Medical Monitor b. Findings which would make QTc measurements difficult or QTc data

	uninterpretable c. History of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome) 13. History of alcoholism or drug/chemical abuse. 14. Unwilling to abstain from alcohol consumption within 24 hours of check-in to the CRU on Day -1 throughout the study. 15. Positive urine drug screen (including cotinine, cannabinoids, amphetamines, cocaine, opiates, benzodiazepines, or barbiturates) at screening or check-in, or positive urine alcohol screen at check-in to the CRU on Day -1. 16. Positive hepatitis panel and/or positive human immunodeficiency virus test at screening. 17. Any of the following hematology values at screening or check-in to the CRU on Day -1, as confirmed by 1 repeat if necessary: a. Hemoglobin <11 g/dL for females, and <12 g/dL for males b. Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L (<1500/μL). c. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), or total bilirubin >1.5 × upper limit of normal (ULN) at screening or check-in to the CRU on Day -1, confirmed by 1 repeat if necessary. 18. Participation in a clinical study involving administration of an investigational drug (new chemical entity) or medical device within the last 90 days or 5 half-lives of the investigational medication, whichever is longer, prior to dosing. 19. Use or intention to use any prescription or nonprescription medications/products within 14 days or 5 half-lives of the medication/product, whichever is longer, prior to check-in to the CRU on Day -1 (hormone replacement therapy or intrauterine contraceptives are acceptable). 20. Receipt of blood products within 2 months prior to check-in to the CRU on Day -1. 21. Donation of blood (>400 mL) or comparable blood loss (>350 mL) from 3 months prior to screening, plasma donation from 2 weeks prior to screening, or platelets donation from 6 weeks prior to screening. 22. Poor peripheral venous access. 23. Consumption of any foods or beverages containing Seville-type oranges, grapefruit, or poppy seeds within 7 days prior to check-in to the CRU on Day -1. 24. Subjects who, in the opinion of the Investigator (or designee; including input from subjects' general practitioner, as applicable), should not participate in this study. 25. Subject hospitalized for any reason in a period of 30 days before the start of the study. 26. Diagnosis with a primary muscle disorder. 27. The presence of any medical device which may interfere with or be impacted by magnetic stimulation. 28. History of any suicidal behavior in lifetime or suicidal ideation within the last 2 years, with or without a plan at screening or check-in (Day –1). 29. Subjects who are investigational site staff members or directly involved in the conduct of the study and their family members or subjects who are employed by the Sponsor. 30. An IPSS score equal to or greater than 6 at check-in
Safety Variables:	Safety assessments will include physical and neurological examinations, vital signs, ECG, Echocardiography, Spirometry, urinary system ultrasound, and laboratory assessments, with telemetry and digit oximetry monitored for the duration of the study. Adverse events will be collected from first dose through the follow-up telephone call (Day 7 for subjects in all SAD level cohorts; Day 12 for subjects in the SAD Level 2,

	Two-Dose cohort; Day 20 for subjects in MAD level cohorts 1–3 and optional MAD level cohort 4). **Adverse Events of Special Interest (AESIs)** The myosin-2 isoform is present in fast-twitch skeletal muscles and the extra-ocular muscles could be affected by MTR-601. Oculofacial AEs or any reduction in movement of the eyes, with potential for disconjugate gaze and "dizziness" or "imbalance" will be noted as an AESI. Additionally, AEs relating to swallowing or proximal muscle weakness (evaluated as part of the routine neurological examination) will be noted as an AESI. In addition, AE's relating to difficulties in urination (evaluated with the IPSS questionnaire and urinary system ultrasound) will be noted as an AESI.
Statistical Analyses:	**Statistical Methods:** This is a non-powered, dose-finding study. Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum, and maximum. In addition, changes from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. **Safety and Tolerability** Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables. **Pharmacokinetics** Individual plasma concentrations, amounts excreted in urine, concentrations in plasma and derived PK parameters will be listed individually, displayed in appropriate graphics, and summarized using descriptive statistics (including arithmetic mean, standard deviation [STD], geometric mean, median, minimum, maximum, and percent coefficient of variation [CV%]). **Pharmacodynamics** Pharmacodynamic effects will be explored, including effects on muscle strength as a function of dose, exposure, muscle accumulation (with potential adjustments for total body muscle mass/composition).
Sample Size Determination:	This is a single center study conducted at 1 site and will enroll up to approximately 88 subjects. This sample size accommodates withdrawal of consent or replacement for other non-TEAE reasons and is appropriate for dose escalation studies of this nature.

1.2. Study Schema

SAD and MAD Schematic:



Motric Bio Study Scheme: Cohorts of 8 participants (6 MTR-601 and 2 placebo) will be sequentially enrolled following evaluation of safety and tolerability (S and T) by a Safety Review Committee (SRC). The SRC will determine whether any dose is safe and tolerable by evaluation of aggregate clinical, laboratory, ECG, echocardiography, spirometry, renal/urinary ultrasonography and PK (as available) data. The Single Ascending Dose (SAD) cohorts will begin dosing with 2 sentinel participants (1:1 - MTR-601: Placebo) followed 72 hours later by dosing the remainder of the cohort (5:1 - MTR-601: Placebo). Dosing will be performed after a standard breakfast, in all but one cohort, as preclinical studies indicated food enhanced exposure. The second SAD cohort will receive two doses of study drug – the first dose will be after overnight fasting and the second dose, following a washout period, after a standard breakfast. The Multiple Ascending Dose (MAD) cohorts will not begin until at least the SAD level 2 two-dose cohort has been completed and will not have sentinel dosing. MAD dosing will be daily for 14 days.

1.3. Schedule of Assessments (SAD)

Table 1: Schedule of Assessments Single Ascending Dose (SAD) Level 1, 3, 4 and 5 Cohorts

	Screening	CI	CRU Inpatient															FU
Day	(-30 to -2)	D (-1)	D1											D2	D3	D4	D5		D7
Hour			0	0.25	0.50	1	1.5	2	3	4	6	8	12	0	0	0	0	4	
Informed consent	X																		
Confirm eligibility	X	X[p]																	
Demographics	X																		
Medical history	X	X			F														
Full physical examination	X	X																X	
Neurological exam	X	X																X	
Height/weight [a]	X	X																X	
HIV/Hep B/Hep C	X																		
CRU Check-in		X																	
SARS-CoV-2 PCR [b]		X																	
Drug screen [c]	X	X																	
Laboratory assessments [d]	X	X								X			X	X	X	X	X		
FSH testing [e]	X																		
Urinalysis [f]	X	X								X				X	X	X	X		
Pregnancy test [g]	X	X [g]																	
12-lead electrocardiogram	X	X																X	
Body composition [h]		X																	
C-SSRS	X	X																X	
LVEF/Echocardiogram	X [i]													X					
Randomization			X																
Cardiac telemetry [j]			←										→						
Oximetry [j]			←										→						
Vital signs	X	X	X			X	X			X	X	X	X	X	X	X	X		

	Screening	CI	CRU Inpatient															FU
Day	**(-30 to -2)**	**D (-1)**	**D1**										**D2**	**D3**	**D4**	**D5**		**D7**
Hour			**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**0**	**0**	**0**	**0**	**4**	
Plasma PK [k]			←	←	←	←	←	←	←	←	←	←	←	←	←	←	X		
Urine PK [l]			X							X		X	X	X	X	X	X		
Genetic biomarker (buccal swab)		X																	
Plasma Biomarker sample			X			X								X			X		
Spirometry		X								X			X	X	X		X		
Magnetic stimulated contraction		X								X				X			X		
Dynamometry		X								X		X	X	X	X	X	X		
Muscle biopsy [m]														X					
IPSS [n]		X												X	X	X	X		
Urinary System Ultrasound [o]		X													X		X		
MTR-601 administration			X																
Adverse events			←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Concomitant medications	X		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
CRU check-out/discharge																		X	
Follow-up telephone call																			X

Abbreviations: AE = adverse event; CK-MB = creatinine kinase heart; CK-MM = creatinine kinase skeletal muscle; CRU = clinical research unit; D = Day; Hep = hepatitis; HIV = human immunodeficiency virus; LVEF = left ventricular ejection fraction; PCR = polymerase chain reaction; PK = pharmacokinetics; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: When several assessments overlap, the suggested sequence of events will be as follows: ECG, vital sign collection, PK sample collection, laboratory blood sample collections, spirometry, dynamometry, urinalysis sample collection, and biopsy such that PK sample collection will be drawn as close to the nominal collection time point as possible.

a. Height measured only at screening.
b. To be performed as part of check-in procedures, prior to other Day -1 activities
c. Urine drug screen for cotinine, alcohol, and drugs of abuse.
d. Laboratory assessments will include serum chemistry, hematology, liver function tests, coagulation, and creatinine kinase (CK-MM and CK-MB). eGFR will use CKD-EPI calculation. For Cohort 4 only, Cystatin C will be measured on Day 1 at 4 and 12 hours post dose, and on Day 2.

e. FSH testing for postmenopausal females only.
f. Urinalysis by dipstick; if results are abnormal, follow up with microscopy. Samples are to be collected under colored lighting into opaque containers to blind participants to any discoloration of the urine.
g. For women of childbearing potential: Serum pregnancy test at screening.
h. Body composition assessments by bioimpedance and physical measurements.
i. Performed during screening as a secondary visit or up to Day -1 check-in to confirm subject is still eligible.
j. Telemetry and oximetry will continue into approximately 24 hour timepoint (Day 2), although it may be interrupted as needed to allow subjects to bathe.
k. Plasma PK samples will be drawn at pre-dose (time 0); post-dose on Day 1 at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, and 12hours; 24 hours post-dose (Day 2); 48 hours post-dose (Day 3);
72 hours post-dose (Day 4); and 96 hour post-dose (Day 5).
l. Urine will be collected for PK analysis on Day 1 from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, 8–12 hours, and 12–24 hours; from 24–48 hours post-dose; from 48–72 hours post-dose ; and from 72–96 hours post-dose . Samples are to be collected at intervals under amber-colored lighting into opaque containers to blind participants to any discoloration of the urine.
m. Mandatory muscle biopsy on Day 2 only.
n. IPSS questionnaire will be performed at the specified timepoints per SOA- results greater than 8 will necessitate an unscheduled urinary system ultrasound as soon as is feasible.
o. Urinary system Ultrasound will be performed at specified timepoints in SOA unless the IPSS result (greater than 8) necessitates additional unscheduled ultrasonography.
p. Screening eligibility will be determined by off-site (LabCorp) lab Total CK and CK-MB values and normal ranges while check-in eligibility will be determined by Day-1 on-site (WCT) lab Total CK and CK-MB values and normal ranges. Furthermore, CK isoenzymes (e.g., MM, MB) will not be evaluated as part of dose escalation decisions – rather total CK will be used.

1.4. Schedule of Assessments (SAD, Level 2, Two-Dose)

Table 2: Schedule of Assessments SAD Level 2, Two-Dose Cohort – Screening/Check-in/Day 1/Washout

	Screening	CI	CRU Inpatient														
Day	**(-30 to -2)**	**D (-1)**	**D1**										**D2**	**D3**	**D4**	**D5**	
Hour			**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**← Washout →**			
Informed consent	X																
Confirm eligibility	X[o]	X															
Demographics	X																
Medical history	X	X															
Full physical examination	X	X															X
Neurological exam	X	X															X
Height/weight [a]	X	X															X
HIV/Hep B/Hep C	X																
CRU Check-in		X															
SARS-CoV-2 PCR [b]		X															
Drug screen [c]	X	X															
Laboratory assessments [d]	X	X								X			X	X	X	X	X
FSH testing [e]	X																
Urinalysis [f]	X	X								X				X	X	X	X
Pregnancy test [g]	X	X															
12-lead electrocardiogram	X	X															X
Body composition [h]		X															
C-SSRS	X	X															X
LVEF/Echocardiogram	X [i]													X			
Randomization			X														
Cardiac telemetry [j]			←										→				
Oximetry [j]			←										→				
Vital signs	X	X	X			X	X			X	X	X	X	X	X	X	X

	Screening	CI	CRU Inpatient													
Day	**(-30 to -2)**	**D (-1)**	**D1**										**D2**	**D3**	**D4**	**D5**
Hour			**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**← Washout →**			
Plasma PK [k]			←													→
Urine PK [l]			X							X		X	X	X	X	X	X
Genetic biomarker (buccal swab)		X															
Plasma Biomarker			X			X								X			
Spirometry		X								X			X	X	X		X
Electronic nerve stimulation response		X								X				X			X
Dynamometry		X								X		X	X	X	X	X	X
IPSS [m]		X												X	X	X	X
Urinary system Ultrasound [n]		X													X		
MTR-601 administration			X														
Adverse events			←														→
Concomitant medications	X	X	←														→

Abbreviations: AE = adverse event; CI = Check-in; CK-MB = creatinine kinase heart; CK-MM = creatinine kinase skeletal muscle; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; LVEF = left ventricular ejection fraction; PK = pharmacokinetics.
Note: When several assessments overlap, the suggested sequence of events will be as follows: ECG, vital sign collection, PK sample collection, laboratory blood sample collections, spirometry, dynamometry, urinalysis sample collection, and biopsy, such that PK sample collection will be drawn as close to the nominal collection time point as possible.

a. Height measured only at screening.
b. To be performed as part of check-in procedures, prior to other Day -1 activities
c. Urine drug screen for cotinine, alcohol and drugs of abuse.
d. Laboratory assessments will include serum chemistry, hematology, liver function tests, coagulation, and creatinine kinase (CK-MM and CK-MB). eGFR will use CKD-EPI calculation.
e. FSH testing for postmenopausal females only.
f. Urinalysis by dipstick; if results are abnormal, follow up with microscopy. Samples are to be collected under colored lighting into opaque containers to blind participants to any discoloration of the urine.
g. For women of childbearing potential: Serum pregnancy test.
h. Body composition assessments by bioimpedance and physical measurements (after negative SARS-CoV-2 test results).
i. Performed during screening as a secondary visit or up to Day -1 to confirm subject is still eligible.

j. Telemetry and oximetry will continue into approximately 24 hour timepoint (Day 2) although it may be interrupted as needed to allow subjects to bathe.
k. Plasma PK samples will be drawn at pre-dose (time 0); post-dose on Day 1 at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, and 12hours; 24 hours post-dose (Day 2); 48 hours post-dose (Day 3); and 72 hours post-dose (Day 4).
l. Urine will be collected for PK analysis on Day 1 from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, 8–12 hours, and 12–24 hours; from 24–48 hours post-dose ; from 48–72 hours post-dose ; and from 72–96 hours post-dose. Samples are to be collected at intervals under colored lighting into opaque containers to blind participants to any discoloration of the urine.
m. IPSS questionnaire will be performed at the specified timepoints per SOA- results greater than 8 will necessitate an unscheduled urinary system ultrasound as soon as is feasible.
n. Urinary system Ultrasound will be performed at specified timepoints in SOA unless the IPSS result (greater than 8) necessitates additional unscheduled ultrasonography.
o. Check-in eligibility will be determined by Day-1 on-site Total CK and CK-MB, not by Day -1 outside laboratory Total CK and isoenzymes.

Table 2 continued… Schedule of Assessments SAD Level 2, Two-Dose Cohort – Days 6–10 and Follow-up

	CRU Inpatient																FU
Day	D6											D7	D8	D9	D10		D12
Hour	0	0.25	0.50	1	1.5	2	3	4	6	8	12	0	0	0	0	4	
Full physical examination															X		
Neurological exam															X		
Height/weight															X		
Laboratory assessments [a]								X			X	X	X	X	X		
Urinalysis [b]	X					X		X		X	X	X	X	X	X		
12-lead electrocardiogram															X		
C-SSRS																X	
LVEF/Echocardiogram												X					
Cardiac telemetry [c]	←											→					
Oximetry [c]	←											→					
Vital Signs	X			X	X			X	X	X	X	X	X	X	X		
Plasma PK [d]	←														→		
Urine PK [e]	X							X		X	X	X	X	X	X		
Spirometry								X			X		X		X		
Electronic nerve stimulation response								X				X			X		
Muscle biopsy [f]												X					
Dynamometry								X		X	X	X	X	X	X		
Plasma Biomarker	X			X								X			X		
IPSS [g]									X			X	X	X	X		
Urinary system Ultrasound [h]													X		X		
MTR-601 administration	X																
Adverse events	→																
Concomitant medications	→																

	CRU Inpatient																FU
Day	**D6**											**D7**	**D8**	**D9**	**D10**		**D12**
Hour	**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**0**	**0**	**0**	**0**	**4**	
CRU check-out/discharge																X	
Follow-up telephone call																	X

Abbreviations: AE = adverse event; CI = Check-in; CK-MB = creatinine kinase heart; CK-MM = creatinine kinase skeletal muscle; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; LVEF = left ventricular ejection fraction; PK = pharmacokinetics.
Note: When several assessments overlap, the suggested sequence of events will be as follows: ECG, vital sign collection, PK sample collection, laboratory blood sample collections, spirometry, dynamometry, urinalysis sample collection, and biopsy, such that PK sample collection will be drawn as close to the nominal collection time point as possible.

a. Laboratory assessments will include serum chemistry, hematology, liver function tests, coagulation, and creatinine kinase (CK-MM and CK-MB). eGFR will use CKD-EPI calculation
b. Urinalysis by dipstick; if results are abnormal, follow up with microscopy. Samples are to be collected at intervals under colored lighting into opaque containers to blind participants to any discoloration of the urine.
c. Telemetry and oximetry will continue for approximately 24 hours post-dose (Day 7) although it may be interrupted as needed to allow subjects to bathe.
d. Plasma PK samples will be drawn at pre-dose (time 0); post-dose on Day 1 at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8 and 12 hours; 24 hours post-dose (Day 7); 48 hours post-dose (Day 8); 72 hours post-dose (Day 9); and 96 hours post-dose (Day 10).
e. Urine will be collected for PK analysis on Day 6 from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, 8–12 hours, and 12–24 hours; from 24–48 hours post-dose; from 48–72 hours post-dose; and from 72–96 hours post-dose . Samples are to be collected at intervals under colored lighting into opaque containers to blind participants to any discoloration of the urine.
f. Mandatory muscle biopsy on Day 7 (time 0) only.
g. IPSS questionnaire will be performed at the specified timepoints per SOA- results greater than 8 will necessitate an unscheduled urinary system ultrasound as soon as is feasible.
h. Urinary system Ultrasound will be performed at specified timepoints in SOA unless the IPSS result (greater than 8) necessitates additional unscheduled ultrasonography.

1.5. Schedule of Assessments (MAD)

Table 3: Schedule of Assessments Multiple Ascending Dose Level Cohorts 1 – 6 (MAD) – Screening/Check-in/Day 1

	Screening	CI	CRU Inpatient										
Day	**(-30 to -2)**	**D (-1)**	**D1 – Initial Dosing Day**										
Hour			**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**
Informed consent	X												
Confirm eligibility	X	X[o]											
Demographics	X												
Medical history	X	X											
Full physical examination	X	X											
Neurological examination	X	X											
Height/weight [a]	X	X											
HIV/Hep B/Hep C	X												
CRU Check-in		X											
SARS-CoV-2 PCR [b]		X											
Drug screen [c]	X	X											
Laboratory assessments [d]	X	X								X			X
Urinalysis [e]	X	X								X			
FSH testing [f]	X												
Pregnancy test [g]	X	X											
12-lead electrocardiogram	X	X											
Body composition [h]		X											
C-SSRS	X	X											
LVEF/Echocardiogram	X [i]												
Randomization			X										
Cardiac telemetry [j]			←	←	←	←	←	←	←	←	←	←	←
Oximetry [j]			←	←	←	←	←	←	←	←	←	←	←

	Screening	CI	CRU Inpatient										
Day	**(-30 to -2)**	**D (-1)**	**D1 – Initial Dosing Day**										
Hour			**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**
Vital signs	X	X	X			X	X			X	X	X	X
Plasma PK [k]			←	←	←	←	←	←	←	←	←	←	←
Urine PK [l]			X							X		X	X
Genetic biomarker (buccal swab)		X											
Plasma Biomarker			X			X							
Spirometry		X								X			X
Magnetic stimulated contraction[p]		X								X			
Dynamometry[p]		X								X		X	X
IPSS [m]		X											
Urinary system Ultrasound [n]		X											
MTR-601 administration			X										
Adverse events			←	←	←	←	←	←	←	←	←	←	←
Concomitant medications	X	X	←	←	←	←	←	←	←	←	←	←	←

Abbreviations: AE = adverse event; CI = Check-in; CK-MB = creatinine kinase heart; CK-MM = creatinine kinase skeletal muscle; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; LVEF = left ventricular ejection fraction; PK = pharmacokinetics.
Note: When several assessments overlap, the suggested sequence of events will be as follows: ECG, vital sign collection, PK sample collection, laboratory blood sample collections, spirometry, dynamometry, urinalysis sample collection, and biopsy, such that PK sample collection will be drawn as close to the nominal collection time point as possible.

a. Height measured only at screening.
b. To be performed as part of check-in procedures, prior to other Day -1 activities.
c. Urine drug screen for cotinine, alcohol, and drugs of abuse.
d. Laboratory assessments will include serum chemistry, hematology, liver function tests, coagulation, and creatinine kinase (CK-MM and CK-MB). eGFR will use CKD-EPI calculation. For Cohort 3 only, Cystatin C will be measured on Day 1 at 4 and 12 hours and Day 2, Day 8 and Day 14 (all pre-dose).
e. Urinalysis by dipstick; if results are abnormal, follow up with microscopy. Samples are to be collected under colored lighting into opaque containers to blind participants to any discoloration of the urine. For Cohort 3 only, urine creatinine, protein, albumin and Kim-1 will be measured at Day -1, Day 1 at 4 hours, Day 15 and Day 16; and urine sediment will be microscopically evaluated at Day -1, Day 7 (pre-dose) and Day 15.
f. FSH testing for postmenopausal females only.
g. For women of childbearing potential: Serum pregnancy test.
h. Body composition assessments by bioimpedance and physical measurements.
i. Performed during screening as a secondary visit or up to Day -1 to confirm subject is still eligible.
j. Telemetry and oximetry will continue into approximately 24 hours post-dose (Day 2), although it may be interrupted as needed to allow subjects to bathe.

k. Plasma PK samples for Day 1 (initial dosing day) will be drawn at pre-dose (time 0); and post-dose at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, and 12 hours.
l. Urine will be collected for PK analysis on Day 1 from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, and 8–12 hours. Samples are to be collected at intervals under colored lighting into opaque containers to blind participants to any discoloration of the urine.
m. IPSS questionnaire will be performed at the specified timepoints per SOA- results greater than 8 will necessitate an unscheduled urinary system ultrasound as soon as is feasible .
n. Urinary system Ultrasound will be performed at specified timepoints in SOA unless the IPSS result (greater than 8) necessitates additional unscheduled ultrasonography.
o. Screening eligibility will be determined by off-site (LabCorp) Lab Total CK and CK-MB values while check-in eligibility will be determined by Day-1 on-site (WCT) lab Total CK and CK-MB values. .Furthermore, CK isoenzymes (e.g., MM, MB) will not be evaluated as part of dose escalation decisions – rather total CK will be used.
p. For Cohorts 4-6, Magnetic Stimulated Contraction and Dynamometry time points will be as follows: Day -1, Day 1 (0-2 hours pre-dose), Day 7, Day 8, Day 12, Day 13, Day 14, Day 15.

Table 3 continued… Schedule of Assessments Multiple Ascending Dose Level Cohorts 1–6 (MAD) – Days 2-18 and Follow-up

	CRU Inpatient																	FU
Day	**Non-PK Days 2–6, 8-13**	**PK Days 7 and 14**											**D15**	**D16**	**D17**	**D18**		**D20**
Hour		**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**0**	**0**	**0**	**0**	**4**	
Full physical examination		X														X		
Neurological exam		X														X		
Height/weight [a]		X														X		
Laboratory assessments [b]	X[k]	X											X	X	X	X		
Urinalysis		X											X	X	X	X		
12-lead ECG		X														X		
C-SSRS									X							X		
LVEF/Echocardiogram	X [c]																	
Cardiac telemetry [d]	→	→	→	→	→	→	→	→	→	→	→	→	→					
Oximetry [d]	→	→	→	→	→	→	→	→	→	→	→	→	→					
Vital signs		X			X	X			X	X	X	X	X	X	X	X		
Plasma PK [e]		→	→	→	→	→	→	→	→	→	→	→	X	X	X	X		
Urine PK [f]	X	X							X		X	X	X	X	X	X		
Biomarker		X														X		
Spirometry	X [g]								X			X		X		X		
Magnetic stimulated contraction		X							X				X			X		
Dynamometry	X	X							X		X	X	X	X	X	X		
Muscle biopsy [h]		X																
IPSS [i]	X									X			X	X	X		X	

	CRU Inpatient																	FU
Day	**Non-PK Days 2–6, 8-13**	**PK Days 7 and 14**											**D15**	**D16**	**D17**	**D18**		**D20**
Hour		**0**	**0.25**	**0.50**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**0**	**0**	**0**	**0**	**4**	
Urinary system Ultrasound [j]	X									X						X		
MTR-601 administration	X	X																
Adverse events	→																	
Concomitant medications	→																	
CRU check-out/discharge																	X	
Follow-up telephone call																		X

Abbreviations: AE = adverse event; CK-MB = creatinine kinase heart; CK-MM = creatinine kinase skeletal muscle; D = Day; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; PK = pharmacokinetics.
Note: When several assessments overlap, the suggested sequence of events will be as follows: ECG, vital sign collection, PK sample collection, laboratory blood sample collections, spirometry, dynamometry, urinalysis sample collection, and biopsy, such that PK sample collection will be drawn as close to the nominal collection time point as possible.

a. Height measured only at screening.
b. Laboratory assessments will include serum chemistry, hematology, liver function tests, coagulation, and creatinine kinase (CK-MM and CK-MB). eGFR will use CKD-EPI calculation.
c. Echocardiogram performed on Day 6 and Day 13 only, post AM dosing.
d. Telemetry and oximetry will continue from Day 1 into pre-dose Day 2; Day 7 into pre-dose Day 8; and Day 14 into Day 15, and for 12 hours post dosing on all other dosing days although it may be interrupted as needed to allow subjects to bathe.
e. Plasma PK samples will be drawn at pre-dose (time 0) on Days 7 and 14; post-dose on Days 7 and 14 at 1, 1.5, 2, 4, 6, 8 and 12 hours; (need trough at D14) 336 hours post-dose (Day 15); 360 hours post-dose (Day 16); and 384 hours post-dose (Day 17). For Cohorts 3-6, PK samples will also be drawn on Day 2 and Day 8 (both pre-dose).
f. Urine will be collected for PK analysis on 12-24 hours post-dose on Day 2; Day 7 and 14 from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, 8–12 hours, and 12–24 hours; from 24–48 hours post-dose; from 48–72 hours post-dose; and from 72–96 hours post-dose. Samples are to be collected at intervals under colored lighting into opaque containers to blind participants to any discoloration of the urine.
g. Spirometry performed on Days 2, 8, 10, and 12.
h. Mandatory muscle biopsy on Day 14 (time 0) only.
i. IPSS questionnaire will be performed at the specified timepoints per SOA- results greater than 8 will necessitate an unscheduled urinary system ultrasound as soon as is feasible.
j. Urinary system Ultrasound will be performed at day 3, and days 7 and 14 at the 6-hour timepoint unless the IPSS result (greater than 8) necessitates additional unscheduled ultrasonography.
k. Serum chemistry, eGFR, and calcium only.

2. INTRODUCTION

2.1. Disease Background

Spasticity is a sensorimotor condition reflecting an abnormal increase in muscle tone or stiffness due to prolonged muscle contraction. It is usually caused by brain and spinal cord injuries after stroke or trauma or associated with neurological disorders like cerebral palsy or multiple sclerosis. Spasticity-related physical and mental effects can be severely disabling and render patients unable to walk, work, or carry out basic self-care.

There are multiple treatments available for spasticity, but most are characterized by limited efficacy and multiple side effects. Baclofen, a GABAB agonist, is a common centrally acting treatment for spasticity. While generally preferred as first-line treatment for spasticity, oral baclofen's efficacy is compromised by inefficient blood brain barrier penetration. Additionally, treatment is associated with unwelcome side effects, including systemic muscle relaxation, sedation, drowsiness and hepatotoxicity [1]. Intrathecal baclofen is used to achieve a higher central nervous system concentration and improve efficacy. Tizanidine, an α2 agonist, is sometimes used in conjunction with other oral drugs, like baclofen, but it's use is also limited by a very short half-life and multiple side effects, including sedation, hypotension, xerostomia, muscle weakness, hallucinations and QT interval prolongation [1]. Peripherally acting dantrolene has been associated with severe hepatotoxicity and its clinical use is limited [1]. Botulinum toxins are used to treat local spasticity, but treatments are painful, costly, inconvenient and often ineffective [2, 3]. Dorsal rhizotomy is a risky surgical treatment reserved for severe cases of spasticity.

Collectively, the limited efficacy and side effect profiles of available spasticity treatments highlight the need for a selective, well-tolerated, and effective oral treatment for spasticity.

MTR-601 directly targets the terminal effector enzyme (fast myosin-2 isoforms) of skeletal muscle contraction and, therefore, should be able to demonstrate efficacy without the neurological and cardiovascular side effect profile of current muscle relaxants. A further advantage of MTR-601-based muscle relaxation over current muscle relaxants is that MTR-601 does not cause complete immobilization even at extremely high doses due to the residual muscle tone from the uninhibited slow myosin-2 isoform fractions in skeletal muscles.

2.2. Overview of MTR-601

MTR-601 is a small-molecule inhibitor of myosin-2 "fast" isoforms being developed by Motric Bio, Inc. (Motric) for the treatment of muscle spasticity associated with neurological injury or disease. MTR-601 selectively stabilizes the actin unbound conformation of myosin-2 isoforms that have a leucine at position 476 instead of a phenylalanine. Selective targeting is essential as myosin isoforms in skeletal muscle and heart muscle are structurally similar. The selectivity of MTR-601 spares "slow" isoforms found in cardiac and smooth muscle [4].

The proposed MTR-601 development program relies on prior nonclinical data acquired from Motor Pharma who began development of the investigational compound (known to Motor Pharma as MPH-220) as well as nonclinical studies sponsored by Motric. Nonclinical studies

have indicated that MTR-601 selectively inhibits fast skeletal myosin-2. As such, it can reduce skeletal muscle force in healthy rats and improve spasticity and gait in rat models of brain injury.

Further, it reduces generalized muscle contractions and the consequent muscle damage in epilepsy models at doses shown to be safe and tolerable in preliminary non-GLP dose-range-finding (DRF) toxicology studies. A full package of nonclinical safety pharmacology and toxicology studies is ongoing for MTR-601 via the oral gavage route and in compliance with International Council for Harmonisation (ICH) M3(R2) guidelines. Additional supporting in vitro pharmacology and drug metabolism and pharmacokinetic (PK) studies will also be included in the initial IND submission. Proposed study MTR601-NHV-101 will be the first-in-human (FIH) study for MTR-601 to be conducted in normal, healthy volunteers. Later development will focus on conditions characterized by hypertonia and/or spasticity such as, but not exclusively, cerebral palsy, in multiple age ranges.

2.3. Nonclinical Studies and Interim Safety Analysis

Refer to the Investigator's Brochure (IB) or MTR-601 regarding nonclinical study data.

An unblinded interim safety analysis of SAD cohorts 1-4 and MAD cohorts 1-3 was performed to support further dose escalation above the $1/10^{th}$ rat 28-day NOAEL level (where MAD dosing had been capped by the FDA). The key conclusions from that interim analysis were:

- In either single doses (10, 20, 40 and 80 mg) or repeat daily doses (10 and 20 mg for 14 days) MTR-601 did not demonstrate pharmacodynamic evidence of decreased muscle strength. This is likely because the achieved muscle concentrations (≤937 ng/mL) were below the estimated target for efficacy (≥3,000 ng/dL). Further dose escalation is required to adequately characterize MTR-601's pharmacodynamic effect.
- In both single and multiple doses, MTR-610 plasma pharmacokinetics were consistent and predictable, with linear dose-exposure proportionality, and modest (<2-fold) accumulation at steady state. At the 20 mg level, steady state exposure (C_{max} and AUC_{0-24}) was approximately $1/15^{th}$ of the NOAEL. MTR-601's well-behaved pharmacokinetics allows for reliable prediction of exposure for careful, continued dose escalation.
- In both single and multiple doses, MTR-601 was safe and very well tolerated, with no treatment-related AEs, and no clinically significant laboratory, ECG, or vital sign abnormalities. There were no MTR-601 associated abnormalities in plasma or urine markers of kidney function, and no objective or subjective evidence of urinary obstruction. This very good safety profile justifies continued dose escalation to more fully characterize MTR-601's clinical profile.

The findings of the interim safety evaluation support continued dose escalation to more fully characterize the PK, PD and safety of MTR-601.

2.4. Study Rationale

MTR-601 is an oral, small-molecule drug intended to selectively inhibit the isoform of myosin-2 found in fast-twitch skeletal muscle but not the myosin isoforms found in smooth or cardiac

muscle. The clinical objective is to reduce hypertonicity and spasticity in skeletal muscle from primary muscular disease and/or secondary to neurologic injury.

The current study is a FIH evaluation of MTR-601 and focuses on the safety, tolerability, and pharmacokinetics (including uptake into skeletal muscle) of the drug in normal healthy volunteers. Exploratory assessments of effects on the force of muscular contraction will also be performed and evaluated as it relates to dose, exposure, and/or muscle accumulation with potential adjustments for total body muscle mass.

As a FIH study, this will be conducted in normal healthy volunteers in the fed state, with further evaluation of food effect in SAD dose level 2, as nonclinical studies have indicated that food increases drug exposure.

The evaluations of effects on muscular contraction with potential adjustments for total body muscle mass will help guide dosing selection in adult and potential pediatric patient populations in subsequent clinical studies.

2.5. Benefit/Risk Assessment

There will be no direct benefits to normal healthy volunteers being enrolled in this FIH study.

Safety is predicated on the enabling, nonclinical Good Laboratory Practice (GLP) safety and toxicology studies. In addition, during the clinical study, extensive safety evaluations of biochemical, hematologic, renal and urinary systems, cardio-respiratory parameters, as well as clinical evaluations, will be performed. A two-stage dosing strategy with sentinel participants will limit exposure to the investigational agent as dosing is advanced.

To fully evaluate the PK and pharmacodynamic (PD) aspects of MTR-601, subject's will be asked to undergo a single needle biopsy of skeletal muscle (vastus lateralis) using a Bard Magnum 12 gauge or functionally similar hand-held, spring-loaded device (in conjunction with local anesthesia and skin disinfection), potentially requiring 2 collections, which is minimally invasive and commonly used in clinical trials. The risks of such a procedure are discomfort/pain and possibly some small post-procedure bleeding. Any adverse reactions will be appropriately attended to by the unit medical staff.

The myosin-2 isoform is present in fast-twitch skeletal muscles and the extra-ocular muscles could be affected by MTR-601. Oculofacial AEs or any reduction in movement of the eyes, with potential for disconjugate gaze and/or possible "dizziness" or "imbalance" will be noted as an AESI. Additionally, AEs relating to swallowing or proximal muscle weakness (evaluated as part of the routine neurological examination) will be noted as an AESI. Nonclinical studies in the rat but not the dog showed urinary symptomatology not expected in humans, but out of an abundance of caution, any AE relating to difficulties in urination (evaluated with the IPSS questionnaire and urinary system ultrasound) will be noted as an AESI.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the safety and tolerability of single and multiple doses of MTR-601 in normal healthy volunteers under fed and fasted conditions.	The primary endpoint is safety assessed after single and multiple dose administration by: • Incidence, severity, and relatedness of adverse events (AEs; number and incidence of treatment-emergent adverse events [TEAEs]) • Incidence of laboratory abnormalities, based on hematology, clinical chemistry, coagulation, urinalysis test results • Vital sign measurements • 12-lead electrocardiograms (ECGs) • Echocardiography • Physical and neurological examinations • Telemetry and oximetry • Spirometry • Urinary system Ultrasound
Secondary	
To evaluate the plasma and urine pharmacokinetics (PK) of MTR-601	Pharmacokinetic evaluations may include: • Concentration-time relationships • Estimations of dose proportionality at steady state • Estimation of time to achieve steady state • Potential MTR-601 metabolites
[redacted]	[redacted]
Exploratory	

Muscle accumulation of MTR-601 by muscle biopsy and other potential mechanistic, predictive and PD markers of MTR-601	• An evaluation of concentration-effect relationships with other parameters (e.g., cytochrome P450 isoenzymes that affect absorption, distribution, metabolism, and excretion [ADME], other muscle parameters, gender, etc.) that may be performed at a later date and described in a stand-alone analysis plan and report • Muscle accumulation assessed by muscle biopsy and estimates of body muscle mass • An evaluation of potential MTR-601 PD and/or predictive biomarkers may be conducted (genetic and/or protein endpoints)

4. STUDY DESIGN

4.1. Overall Design

This randomized, placebo-controlled, FIH study of MTR-601 in normal healthy volunteers will consist of 5 single ascending dose (SAD) level cohorts (including 1 SAD Level 2 Two-Dose cohort), and up to 6 multiple ascending dose (MAD) level cohorts, each comprised of 8 subjects (6 MTR-601; 2 placebo). The total sample size will be up to 88 subjects to accommodate withdrawal of consent or replacement for other non-TEAE reasons.

Table 4: SAD/MAD Dose Level Cohorts

SAD/MAD Cohort [a & b]	Dose [g]	Fasted	Fed Standard [c]	N [e]
SAD Level 1	10 mg		✓	8 [f]
SAD Level 2, Two-Dose [d]	20 mg	✓	✓	8 [f]
SAD Level 3	40 mg		✓	8 [f]
SAD Level 4 (Optional)	80 mg		✓	8 [f]
SAD Level 5	160 mg		✓	8
MAD Level 1	10 mg		✓	8
MAD Level 2	20 mg		✓	8
MAD Level 3	20 mg		✓	8
MAD Level 4	40 mg		✓	8
MAD Level 5	80 mg		✓	8
MAD Level 6	≤160 mg		✓	8

Abbreviations: MAD = multiple ascending dose; N = number of subjects; SAD = single ascending dose. Fasted: Subjects will remain NPO (clear liquids allowed) for at least 8 hours prior to dosing.

a. Subjects will participate in only 1 dose level cohort in either the SAD, Two-Dose, or MAD portions of the study.

b. All subjects, regardless of cohort, will have doses administered with staggered timing such that no subjects shall be dosed simultaneously.

c. Subjects will be fed a standard (not high-fat) breakfast 30 minutes before dosing.

d. Subjects in the SAD Level 2, Two-Dose cohort: For the first dose, subjects will be fasting; for the second dose, subjects will be fed a standard not-high fat breakfast 30 minutes before dosing.

e. 6 MTR-601 and 2 placebo per cohort.

f. All SAD dose cohorts (including Level 2, Two-Dose) will have 2 sentinel subjects followed at least 72 hours later by the remaining 6 subjects.

g. Cohort dose may be modified by the Sponsor based upon pharmacokinetic and safety results from earlier cohorts.

SAD Levels 1–5 dosing:

- Each of the SAD dose level cohorts will have 2 sentinel subjects followed at least 72 hours later by the remaining 6 subjects in 1 or more groups, in a staggered fashion. Both sentinel subjects will be evaluated for 72 hours by the Investigator for safety prior to dosing the cohort's remaining 6 subjects.
- Dosing will begin at dose Level 1 (10 mg).

- Subjects in SAD Levels 1, 3, 4 and 5 will be dosed in a fed state (standard non-high-fat breakfast).
- Subjects in the SAD Level 2 Two-Dose (20mg) will be dosed in a fasting state on Day 1 with a subsequent 4-day washout period, followed by dosing in a fed state (standard not-high fat breakfast) on Day 6.
- SAD Level 4 (80 mg) dosing is optional and may be adjusted based upon PK and safety results from earlier cohorts.
- Subjects may be enrolled in small groups to accommodate clinic scheduling.

MAD Levels 1–6 dosing:

- The MAD portion of the study will commence at MAD Level 1 (10 mg) after the safe completion of the subjects in at least the 2 SAD Level 2 Two-Dose cohort.
- Subjects in MAD Levels 1–6 will be dosed in a fed state (standard non-high-fat breakfast) over 14 continuous days of dosing.
- MAD cohorts may be enrolled in small groups to accommodate clinic scheduling with subjects dosed in a staggered fashion.

Dose Escalation:

The study will be monitored by a Safety Review Committee (SRC) comprised of the Principal Investigator (PI), the Medical Monitor, and the Sponsor. The SRC is intended to ensure treatment does not pose undue risk to subjects. Dose escalation to the next higher dose level cohort will not take place until the SRC has assessed the data from at least 7 out of 8 subjects/cohort through discharge (supplemental plasma PK information on a previously treated cohort may be requested as a part of the review) and determined that adequate safety and tolerability has been demonstrated to permit proceeding.

The planned dose levels for MAD Cohort 5 (80 mg) and Cohort 6 (160 mg) may be decreased based on the plasma PK from the preceding MAD cohort. Escalation will proceed no higher than a dose that is estimated to yield ≤ ½ of the rate 28-day NOAEL exposure (C_{max} ≤ 421 ng/mL, AUC_{0-24} ≤ 6,600 ng*hr/mL).

The SRC may recommend:

- Ascending to the planned next higher dose level
- Ascending to a dose level lower than the planned next higher dosage level cohort
- Repeat dosing at the current dose level
- Descending to an intermediate dose above a previously tolerated dose level
- Pausing dose escalation
- Stopping the study

Participation in the clinical study may be discontinued by an Investigator (or delegate) in charge of the study or by the Sponsor for any of the following reasons in Table 5.

Table 5: Stopping Rules

Stopping Rules[d]	Individual Subject Stopping Rules[a]	Cohort and/or Dose Escalation Stopping Rules
ALT or AST ≥3 × ULN	≥1 subject	N/A
ALT or AST >5 × ULN	N/A	≥2 subjects
Creatinine >1.2 × ULN or an increase in serum creatinine by ≥30 µmol/L within 24 hours or an increase in serum creatinine to ≥1.5 × baseline within 7 days	≥1 subject	≥2 subjects
QTcB and QTcF >500 msec or change from baseline: QTc >60 msec	≥1 subject	≥2 subjects
Sustained heart rate <45 bpm or heart rate > 130 bpm [b] confirmed by repeat after 30 minutes	≥1 subject	≥2 subjects
Sustained systolic blood pressure <80 or systolic blood pressure >155 mmHg confirmed by repeat after 30 minutes	≥1 subject	≥2 subjects
Sustained diastolic blood pressure >100 mmHg confirmed by repeat after 30 minutes	≥1 subject	≥2 subjects
Occurrence of a serious adverse event (SAE) in a participant not receiving placebo	≥1 subject	≥1 subject
Severe AEs in the same cohort	N/A	≥1 subject
Clinically significant laboratory abnormalities of the same character	N/A	≥2 subjects
Confirmed lower urinary tract obstruction[c] (Two successive post-void residual volume determinations within 24 hours exceeding 100 mL) or evidence of hydronephrosis upon Ultrasound evaluation.	≥1 subject	≥1 subjects
A drop in the eGFR below 70 mL/min/1.73 m^2 (CKD-EPI) or a reduction of 25% from baseline.	≥1 subject	≥2 subjects
A confirmed[e] reduction in the FVC (forced vital capacity done in triplicate) to less than 80% of the predicted vital capacity based on gender, height and age with good expiratory effort as assessed by the Investigator	≥1 subject	≥2 subjects
Any subject who develops gross or microscopic (>5 RBC/HPF) hematuria (unless clearly caused by menses)	≥1 subject	≥2 subjects
Any subject who has signs, symptoms, and urinalysis/dipstick evidence of a clinically significant urinary tract infection	≥1 subject	≥2 subjects

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bpm = beats per minute; mmHg= millimeters of mercury; msec = millisecond; IP = investigational product; N/A = not applicable; QTcB= QT correct with Bazett formula; QTcF = QT interval corrected for heart rate using Fridericia's formula ;ULN = upper limit of normal.

a. When an out-of- range value meeting the stopping criteria is confirmed by a repeat assessment, the principal investigator shall institute any necessary medical or surgical intervention based on his/her clinical judgement and the standard of care for such a condition to ensure the safety of the trial participant. Such intervention may be implemented within the Clinical Research Unit or upon transfer to a local emergency room/hospital as clinically warranted.

b. When resting heart rate is between 60–100 beats per minute, use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

c. If a lower urinary tract obstruction is suspected, a transurethral bladder catheter should be placed at the clinical research unit to confirm obstruction and remain in place if needed to manage bladder drainage.
d. Lab and eGFR values which meet stopping criteria must be confirmed with a repeat measurement.
e. FVC values meeting stopping rule should be confirmed prior to the next scheduled dose. If repeat FVC no longer meets stopping criteria, dosing may continue.

4.1.1. Trial Stopping Rules

The Investigator must contact the Sponsor immediately to discuss whether to suspend dosing if an AE or laboratory abnormalities indicate that continued dosing of subsequent subjects would not be tolerated or would jeopardize the subjects' safety. The Sponsor alone may suspend dosing at any time for any reason.

Clinical trial stopping rules:

- Occurrence of 1 SAE in a participant not receiving placebo.
- Occurrence of 'severe' non-serious adverse reactions in a participant not receiving placebo.
- Occurrence of 1 death in a participant not receiving placebo.
- Occurrence of 1 case of lower urinary tract obstruction (by catheter-confirmed post void residuals) or hydronephrosis (by ultrasound).
- Occurrence of 2 or more subjects with gross hematuria (unless clearly caused by menses).

Occurrence of 2 or more subjects with a decrease of 50% or more in eGFR. If any of the above scenarios occur, the study will be immediately paused. Further discussion will then occur within the SRC, and a safety review will be conducted. Following the SRC review, the study may continue if the Investigator and Sponsor agree it is safe to proceed. If the study is stopped, the maximum tolerated dose (MTD) will be declared at the dose level lower than that escalation dose.

Study Assessments and Procedures Overview:

Safety assessments will include physical and neurological examinations, vital signs, ECG,

Spirometry, Echocardiography, urinary system ultrasound, and laboratory assessments. Adverse events will be collected from first dose through the follow-up telephone call (Day 7 for subjects in all SAD level cohorts; Day 12 for subjects in the SAD Level 2, Two-Dose cohort; Day 20 for subjects in all MAD cohorts.

Telemetry and digit oximetry will be monitored by applying at least 1 hour prior to dose administration and remain on for approximately 24 hours in the SAD cohorts. In MAD cohorts, telemetry and digit oximetry will be monitored for approximately 24 hours starting on Day 1, Day 7, and Day 14, and monitored on all dosing days from pre-dose until 12 hours post-dose for the duration of the study. Telemetry and oximetry will be interrupted to accommodate daily hygienic routines (e.g., showering).

Blood and urine sample collection for PK analysis of MTR-601 will be collected in the clinical research unit (CRU) at specified time points as detailed in the Schedule of Assessments (Table 1, Table 2, and Table 3).

Spirometry measurements will include:

- Forced expiratory volume in one second (FEV_1)
- Forced vital capacity (FVC)
- FEV_1/FVC ratio (FEV_1 divided by FVC)

Dynamometry measurements will include grip strength, upper extremity (forearm extension/flexion), and lower extremity (knee extension in sitting position).

Refer to the Schedule of Assessments (Table 1, Table 2, and Table 3) for details on exact days and times of assessments.

4.1.2. Study Duration

Subjects Planned:	Duration of IP for each subject by dose level cohort:					
Approximately 88	**SAD:**	1 day	**SAD Two-Dose:**	2 days	**MAD:**	14 days

Total study duration for each subject:	
SAD:	A (maximum) 30-day screening period, check-in to the CRU on Day -1, a single dose of study medication on Day 1 with subsequent in-house observation of at least 96 hours [a], check-out/discharge from the CRU, and a telephone follow-up on Day 7. The total duration will be approximately 37 days.
SAD Two-Dose:	A (maximum) 30-day screening period, check-in to CRU on Day -1, a single dose of study medication on Day 1, a 4-day washout period, a second single dose of study medication on Day 6 with subsequent in-house observation of at least 96 hours [a], check-out/discharge from the CRU, and a telephone follow-up on Day 12. The total duration will be approximately 42 days.
MAD:	A (maximum) 30-day screening period, check-in to the CRU on Day -1, daily dosing of study medication on Days 1–14 with subsequent in-house observation of at least 96 hours a after the last dose, check-out/discharge from the CRU, and a telephone follow-up on Day 20. The total duration will be approximately 50 days.

a. If needed (e.g., in the event of AEs), the in-house observation period may be prolonged for safety observation at the discretion of the Investigator, which will extend duration of study participation by the number of additional observation days required.

4.2. Justification for Dose

Nonclinical toxicology studies were performed in dogs (human equivalent dose [HED] of 69.4 mg/kg at the no-observed-adverse effect level [NOAEL]), and rats (HED of 3.2 mg/kg at the NOAEL).

Based on the findings made in the toxicity studies of MTR-601 and on the NOAELs and HEDs identified, the maximum recommended starting dose (MRSD) in humans was estimated according to European Medicines Agency (EMA) guidance. The calculation is summarized in Table 6.

Table 6: Estimation of the Maximum Recommended Starting Dose

	Rat NOAEL (20 mg/kg)	**Dog NOAEL (125 mg/kg)**
Human equivalent dose (HED)	3.2 mg/kg	69.4 mg/kg
Human equivalent dose (HED)/10	0.32 mg/kg	6.94 mg/kg
For 60 kg subject	**19 mg**	416 mg

Abbreviation: NOAEL = no-observed-adverse-effect level.

Based on these results, a maximum starting dose of 20 mg is acceptable. However, in primary pharmacology studies in rat seizure models, repeat doses of MTR-601 as low as 1 mg/kg were shown to provide modest changes in efficacy endpoints; therefore, an additional 2X factor will be applied to account for these observations and provide added measure of safety for initiating single dose trials. As such, a starting dose of 10 mg will be used and dose escalation in the SAD and MAD will proceed at steps of approximately 2-fold for the dosing sequence: 10 mg once daily, 20 mg QD,

40 mg QD, 80 mg QD and 160 mg QD will be the highest dose level evaluated. The top 2 doses of the MAD may be decreased to insure that the predicted exposure does not exceed ½ the NOAEL exposure (C_{max} = 421 ng/mL, AUC $_{0-24}$ = 6,600 ng*hr/mL). Alternative doses (5 mg QD, 15 mg QD, 30 mg QD or 60 mg QD in the SAD and 5 mg QD, 15 mg QD or 30 mg QD in the MAD) may be evaluated if safety or tolerability issues are encountered at the intended doses. Dose selection decisions will be made by an SRC based on safety, tolerability, clinical laboratory data and available pharmacokinetic data.

4.3. End of Study Definition

The end of the study is defined as the date when the last subject has completed the final scheduled procedure shown in the Schedule of Assessments (Table 1, Table 2, and Table 3).

5. STUDY POPULATION

Subject eligibility must be verified prior to enrollment. Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

5.1. Inclusion Criteria

Subjects who meet ALL the following inclusion criteria will be eligible to participate in the study:

1. Willing to adhere to study procedures and provide written informed consent prior to the start of any study procedures.
2. 18–45 years of age at the time of consent and in good physical health based on medical history, physical examination including vital signs, as well as laboratory, electrocardiogram (ECG), Echocardiogram (LVEF in the normal range of 50-70%), normal muscle strength upon physical examination, and spirometry test values.
3. Weight ≥50 kg and body mass index (BMI) <33 kg/m^2.
4. Females or males with female partners must use a medically accepted contraceptive regimen (i.e., condoms with spermicide, abstinence, nonhormonal intrauterine device (IUD), Essure procedure, or diaphragm with spermicide) from at least 30 days prior to first dose through 90 days after the last dose OR females must be of non-childbearing potential, defined as:
    a. Have been surgically sterilized (e.g., bilateral oophorectomy) or hysterectomized at least 6 months prior to screening. Surgical sterilization procedures or hysterectomy must be supported with clinical documentation/medical records made available to the Sponsor and noted in the Relevant Medical History/Current Medical Condition section of the electronic case report form (eCRF).
    b. Be postmenopausal (i.e., must have no regular menstrual bleeding for at least 2 years prior to inclusion). Menopause will be confirmed by a plasma follicle-stimulating hormone (FSH) level of >40 IU/L.
5. Non-smoker and must not have used any tobacco products within 3 months prior to screening.
6. In good physical and mental health as determined by past medical history, physical examination, psychiatric examination, 12-lead ECG, Echocardiography, spirometry, urinary system ultrasound, vital sign measurements, and clinical laboratory evaluations and calculations (e.g., eGFR greater than 90 mL/1.73 m^2) at screening or check-in to the clinical research unit (CRU) on Day -1, as assessed by the Investigator (or designee). Congenital nonhemolytic hyperbilirubinemia; or suspicion of Gilbert's syndrome based on total and direct bilirubin is not acceptable.
7. Has clinical laboratory test results within the reference ranges of the testing laboratory, except for results outside reference ranges that are deemed not clinically significant by the Investigator (or designee) at screening and check-in to the CRU on Day -1.
8. Vital signs are within normal limits after 3 minutes resting in supine position and FVC (measured in the seated position and triplicate averaged) is ≥90% of the predicted value for gender, age and height with good expiratory effort.

5.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from participation in the study:

1. History of, or physical examination findings indicating, clinically significant endocrine, neurological, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal (including any evidence of pre-existing renal disease, obstructive uropathy for any reason, benign prostatic hypertrophy or kidney stones), respiratory, genitourinary, or muscle abnormalities or diseases that, in the opinion of the Investigator, would render the subject being unsuitable for the study.
2. Unwilling or unable to refrain from strenuous exercise for 3 days prior to check-in and during study or elevated total CK, CK-MB, CK isozenymes or myoglobin at screening, or elevated total CK, CK-MB or myoglobin on Day -1.
3. Unwilling to discontinue coffee (containing caffeine) and other caffeine-containing beverages (e.g., sodas, energy drinks) for at least 72 hours before check-in and throughout the entirety of the study.
4. Use of tobacco- or nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 3 months prior to check-in to the CRU on Day -1 and throughout the entirety of the study (urine cotinine levels will be measured during screening for all subjects; subjects with cotinine values greater than 500 ng/mL will be excluded).
5. Requires prescription or non-prescription medications/herbal remedies/supplements of any kind (with the exception of paracetamol/acetaminophen 2 g/day for up to 3 consecutive days) from 14 days prior to the check-in (Day -1) and throughout the entirety of the study; uses or intends to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing.
6. History or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, urinary, hematological, pulmonary, gastrointestinal, neurological, psychiatric, respiratory, or endocrine disorder, unless determined by the Investigator (or designee) and agreed by the Medical Monitor to be not clinically significant.
7. Active or history of metabolic, cardiovascular, or cerebrovascular disease, including hypertension, angina, ischemic heart disease, transient ischemic attacks, bundle branch block, evidence of myocardial ischemia, stroke, and peripheral arterial disease sufficient to cause symptoms and/or require therapy to maintain stable status.
8. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
9. Active neoplastic disease or history of any neoplastic disease within 5 years of screening (except for basal or squamous cell carcinoma of the skin or carcinoma in situ that has been definitely treated with standard of care).
10. Active infection (e.g., sepsis, pneumonia, abscess) or a serious infection (e.g., resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to dosing.
11. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed).

12. Any of the following at screening and/or pre-dose:
    a. Triplicate averaged QT interval corrected for heart rate using Fridericia's formula (QTcF), QRS duration (>120 msec), PR interval (>220 msec) outside of normal limits confirmed by repeat measurement, unless deemed non-clinically significant by PI and agreed by Medical Monitor
    b. Findings which would make QTc measurements difficult or QTc data uninterpretable
    c. History of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome)
13. History of alcoholism or drug/chemical abuse.
14. Unwilling to abstain from alcohol consumption within 24 hours of check-in to the CRU on Day -1 and throughout the study.
15. Positive urine drug screen (including cotinine, cannabinoids, amphetamines, cocaine, opiates, benzodiazepines, or barbiturates) at screening or check-in, or positive urine alcohol screen at check-in to the CRU on Day -1.
16. Positive hepatitis panel and/or positive human immunodeficiency virus test at screening.
17. Any of the following hematology values at screening or check-in to the CRU on Day -1, as confirmed by 1 repeat if necessary:
    a. Hemoglobin <11 g/dL for females, and <12 g/dL for males
    b. Absolute neutrophil count (ANC) <1.5 × 109/L (<1500/µL).
    c. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), or total bilirubin >1.5 × upper limit of normal (ULN) at screening or check-in to the CRU on Day -1, confirmed by
    d. 1 repeat if necessary.
18. Participation in a clinical study involving administration of an investigational drug (new chemical entity) or medical device within the last 90 days or 5 half-lives of the investigational medication, whichever is longer, prior to dosing.
19. Use or intention to use any prescription or non-prescription medications/products within 14 days or 5 half-lives of the medication/product, whichever is longer, prior to check-in to the CRU on Day -1 (hormone replacement therapy or intrauterine contraceptives are acceptable).
20. Receipt of blood products within 2 months prior to check-in to the CRU on Day -1.
21. Donation of blood (>400 mL) or comparable blood loss (>350 mL) from 3 months prior to screening, plasma donation from 2 weeks prior to screening, or platelets donation from 6 weeks prior to screening.
22. Poor peripheral venous access.
23. Consumption of any foods or beverages containing Seville-type oranges, grapefruit, or poppy seeds within 7 days prior to check-in to the CRU on Day -1.
24. Subjects who, in the opinion of the Investigator (or designee; including input from subjects' general practitioner, as applicable), should not participate in this study.
25. Subject hospitalized for any reason in a period of 30 days before the start of the study.
26. Diagnosis with a primary muscle disorder.

27. The presence or use of any medical device which may interfere with or be impacted by magnetic stimulation.
28. History of any suicidal behavior in lifetime or suicidal ideation within the last 2 years, with or without a plan at screening or check-in (Day -1).
29. Subjects who are investigational site staff members or directly involved in the conduct of the study and their family members or subjects who are employed by the Sponsor.
30. An IPSS score equal to or greater than 6 at check-in.

5.3. Subject Enrollment

Subject eligibility must be verified prior to enrollment. Subjects that continue to meet all inclusion criteria and no exclusion criteria will be sequentially assigned a randomization number by the unblinded pharmacist.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but not subsequently enrolled in the study. Any subjects who screen fails will be fully documented in the source documentation. Minimal information required in the source documentation includes a completed informed consent form (ICF), demography, reasons for screen failure, and all results of all assessments and procedures completed prior to the subject being confirmed as a screen failure and any SAE that occurs after completion of the ICF.

Subjects who do not meet the criteria for participation in this study (i.e., screen failures) may be rescreened once after discussion with the Medical Monitor for non-health-of-the-subject reasons (e.g., washout from over-the-counter medication use, positive urine screen for alcohol).

6. STUDY TREATMENT

6.1. Study Treatment Administered

MTR-601, developed by Motric Bio, is provided in an Orange opaque 2-piece hydroxypropyl methylcellulose (HPMC) capsules containing a blend of MTR-601, silicon dioxide and microcrystalline cellulose for oral administration. Each capsule contains either no MTR-601 (placebo), 5 mg of MTR-601 or 20 mg of MTR-601 for oral dosing. which will be administered in either a fed or fasted state as indicated in Table 4 (SAD/MAD Dose Level Cohorts).

6.2. Handling, Storage, and Accountability

MTR-601 Capsules will be shipped and stored at room temperature.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.

Only subjects enrolled in the study may receive study drug, which may only be supplied or administered by authorized site staff. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff. Refer to the Pharmacy Manual for details regarding on-site storage and handling.

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The Investigator or designee will maintain a record of all study drug received and dispensed.

Prior Sponsor authorization is required for the destruction or return of unused study drug, following dosing of all subjects. Sites without adequate standard operating procedures (SOPs) in place to document on-site destruction of study drug must return unused study drug to an appropriate facility as directed by the Sponsor. Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

The study is randomized, double-blind, and placebo-controlled. Subjects will be assigned to randomized treatment by the unblinded pharmacist in a sequential manner using the pre-determined randomization schedule. Subjects, the Sponsor study team, and the Investigator/site staff will be blinded to treatment assignment until after the final subject has completed the study. Unblinded personnel include site pharmacist (or designee), the unblinded pharmacy monitor (to ensure study drug accountability), and the Sponsor's unblinded team.

The sponsor may review unblinded study data from individual subjects or groups of subjects prior to database lock for safety, regulatory or strategic reasons. In each of these instances, the sponsor will document the objective(s), scope and deliverables before the unblinding occurs, and the investigator(s) and subject(s) will remain blinded.

6.4. Treatment Compliance

Subjects will receive MTR-601 or matched placebo directly from the Investigator or designee, under medical supervision. The dose of study drug and subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study

drug. The date and time of each dose administered in the clinic will be recorded in the source documentation.

6.5. Dose Modifications

Dose modifications within individual subjects are not permitted.

6.6. Continued Access to Study Drug after the End of Study

This is a normal healthy volunteer study; there are no plans to provide MTR-601 after the study exposure period is completed.

6.7. Treatment of Overdose

No information regarding overdose of MTR-601 in humans is available. The subject should be closely monitored for signs of toxicity, and the Medical Monitor notified immediately. There is no specific antidote for overdose of MTR-601, and general supportive care should be provided.

6.8. Concomitant Medications and Therapies

Within 30 days prior to the first administration of MTR-601/placebo, subjects may not use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort.

From 14 days prior to check-in (Day -1) until the Follow-up telephone call (Day 7 for subjects in the SAD level cohorts; Day 12 for subjects in the SAD Level 2, Two-Dose cohort; Day 20 for subjects in all MAD level cohorts, subjects are not permitted to use prescription or non-prescription medications/herbal remedies/supplements of any kind, with the exception of paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) if required for the treatment of AEs.

In the event concomitant medication and/or therapy is needed during the study to treat an AE, the medication and/or therapy must be recorded in the eCRF with its generic name, time of administration, dose, route, duration, and the reason for administration. Concomitant therapy may include urethral catheterization at the discretion of the Principal Investigator and within the current standard of care practice for urinary obstruction.

7. DISCONTINUATION OF STUDY TREATMENT, SUBJECT WITHDRAWAL, AND SUBJECT REPLACEMENT

7.1. Discontinuation of Study Treatment

A subject must be discontinued from study treatment for any of the following:

1. Withdrawal of consent to further follow-up assessments, irrespective of the reason. Note: a subject may withdraw consent to receive further study drug but should be requested to allow follow up for safety and collection of other follow up data.
2. Unable to remain under medical supervision.
3. Investigator decision (may include the need for other therapy not otherwise permitted in the study; any clinically relevant sign, symptom, or intercurrent illness that, in the opinion of the Investigator [or designee], warrants subject withdrawal).
4. Noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee).
5. Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee).
6. Has an SAE.
7. Meets any of the hepatotoxicity criteria detailed in Table 5.
8. Death.

The Investigator must contact the Sponsor immediately to discuss whether to suspend dosing if an AE or laboratory abnormalities indicate that continued dosing of subsequent subjects would not be tolerated or would jeopardize the subjects' safety.

7.2. Subject Withdrawal from Study

Study subjects may withdraw from the study at any time for any reason.

A subject will be withdrawn from all study participation (i.e., discontinued without further follow-up) if any of the following criteria are met:

1. Withdrawal of consent to further follow-up assessments, irrespective of the reason. Note: a subject may withdraw consent to receive further study drug but should be requested to allow follow up for safety and collection of other follow up data.
2. Investigator decision (may include the need for other therapy not otherwise permitted in the study; any clinically relevant sign, symptom, or intercurrent illness that, in the opinion of the Investigator [or designee], warrants subject withdrawal).
3. Noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee).

4. Lost to follow-up.

   A subject will be considered lost to follow-up when unable to be contacted by the study site. Only after 3 phone calls (if possible) are attempted and no response received from a certified letter (or equivalent local method) to the subject's last known mailing address should a subject be considered lost to follow-up. All contact attempts should be documented in the subject's source records.

5. Death.
6. Study termination by the Sponsor.

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's eCRF. If a subject is withdrawn, or early terminates from the study, efforts will be made to perform all study assessments as listed in the last day assessments column per Schedule of Assessments for the SAD and MAD – all cohort levels, if possible (see Schedule of Assessments Table 1, Table 2, and Table 3). This is Day 5 for SAD cohorts 1, 3 and 4, Day 10 for SAD cohort 2 and Day 18 for the MAD cohorts 1-4. Other procedures may be performed if merited for subject safety at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in the CRU, these procedures should be performed before discharge, when possible. The Investigator (or designee) may also request that the subject returns for an additional Follow-up visit or consent to an additional Follow-up telephone call. All withdrawn subjects will be followed until resolution of all AEs or until any unresolved AEs are judged by the Investigator (or designee) to have stabilized.

7.3. Subject Replacement

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn because of AEs will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent must be provided before any study-related procedures/assessments are performed.

8.1. General Study Assessments

General study assessments are outlined in Table 7. Not every assessment will be performed at each visit. Refer to the Schedule of Assessments (Table 1, Table 2, and Table 3) for specific procedures/assessments and timing. A separate schedule of permitted visit windows for each procedure/assessment will be provided in the Clinical Monitoring Plan and the Data Management Plan.

Table 7: General Study Assessments

Assessment	Details
Review of inclusion/exclusion criteria	Eligibility is to be confirmed prior to the first dose of study treatment (see Section 5.1 and Section 5.2 for eligibility criteria).
Demographics and medical history	Demographics (age, gender, race, ethnicity), relevant medical history (past and concurrent).
Height and body weight	Height is collected at screening only.
Drug screen	Urine drug screen for drugs of abuse.
Serology	Human immunodeficiency virus (HIV), hepatitis B, hepatitis C; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR).
Prior and Concomitant medication/concomitant therapy	Record all medications that are used from the time that written informed consent has been obtained (or from 14 days prior to the first study medication dose, whichever is longer) throughout the entirety of the study.
Body composition assessments	Body composition assessments by bioimpedance (using the Tanita DC-43OU Total body Composition Analyzer device) and physical measurements (after negative SARS-CoV-2 test results).

8.2. Efficacy Assessments

There are no efficacy assessments in this study.

8.3. Safety Assessments

Safety assessments (Table 8) will include AEs and SAEs, as well as physical examinations, clinical laboratory evaluations, vital sign measurements, spirometry, urinary system ultrasound, Echocardiography, and ECGs. Not every assessment will be performed at each visit. Refer to the Schedule of Assessments (Table 1, Table 2, and Table 3) for specific procedures/assessments and timing. A separate schedule of permitted visit windows for each procedure/assessment will be provided in the Clinical Monitoring Plan and Data Management Plan

Note: When several assessments overlap, the suggested sequence of events will be as follows: ECG, vital sign collection, PK sample collection, laboratory blood sample collections, spirometry, dynamometry, urinalysis sample collection, and biopsy such that PK sample collection will be drawn as close to the nominal collection time point as possible. Echocardiography and Urinary system ultrasounds can be performed last so as to not delay the PK assessments.

Table 8: Safety Assessments

Assessment	Details
AE monitoring	Adverse events will be recorded from the first study medication dose through 14 days after the last follow-up visit/call. AEs will be graded using the scale in Section 8.4.4.3.
Physical examination	Physical examination and review of relevant systems at screening, including body weight and height. Symptom-directed physical examinations and weight measurements are to be performed at other time points or as clinically indicated.
Neurological exam	Includes cranial nerve assessments II-XII, cerebellar function (finger to nose and gait), reflexes (bilateral bicep, patellar, and ankle), gross assessment of extremity strength.
Vital signs	Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
12-lead Electrocardiograms	The QTcF must be recorded for each ECG. All ECGs must be performed in triplicate with at least a 5 minute rest in the supine position with a minimum of 60 seconds in between and the average value will be used for interpretation and AE grade.
Left ventricular ejection fraction (LVEF)/ echocardiogram	An echocardiogram will measure ventricular volumes and left ventricular ejection fraction.
Cardiac telemetry, and oximetry	Telemetry and digit oximetry will be monitored by applying at least 1 hour prior to dose administration and remain on for approximately 24 hours in the SAD cohorts. In MAD cohorts, telemetry and digit oximetry will be monitored for approximately 24 hours starting on Day 1, Day 7, and Day 14, and monitored on all dosing days from pre-dose until 12 hours post-dose for the duration of the study. Telemetry and oximetry will be interrupted to accommodate daily hygienic routines (e.g., showering).

Assessment	Details
Spirometry	Three (3) repetitions with full effort, seated, with approximately 1 minute resting period between each trial (report mean values). A reduction in the vital capacity to less than 80% of the predicted vital capacity with good expiratory effort may suggest diaphragm weakness or paralysis Spirometry measurements will include: Forced expiratory volume in one second (FEV_1). Forced vital capacity (FVC). FEV_1/FVC ratio (FEV_1 divided by FVC). Reference: Graham [5].
Renal function and Urinary tract evaluations	eGFR will be calculated with each serum chemistry determination. Monitoring the renal function tests will include serum creatinine, BUN, Cystatin C (in select cohorts) serum sodium, potassium, calcium, in addition to the above stated eGFR. Ultrasound will be performed to assess post-void bladder volume in excess of 100 mL and for any evidence of hydronephrosis. The ultrasound will include the kidneys, ureter and bladder.
Electronic nerve stimulation response	The stimulation will be provided by MagSTIM200^{2-}and response measured.
Dynamometry	Dynamometry measurements will include: • Grip strength measured with the Jamar device • Upper extremity (forearm extension/flexion) and lower extremity (knee extension in sitting position), measured with the microFET2 device. Measured up to 3 times and record the best effort. Once with good effort is the intent. However, if not deemed a good effort or there is an interruption in the assessment or mistake on the first tries then it can be repeated up to 3 times.
Pregnancy test or FSH	For women of childbearing potential: Serum pregnancy test at screening and day of check-in. For postmenopausal women who are not surgically sterile: FSH testing.
Hematology	Hemoglobin, hematocrit, RBC, WBC with differential (neutrophils [absolute count] and lymphocytes, monocytes, eosinophils, basophils), and platelet count.
Coagulation	PT, INR, aPTT.
Serum chemistry	Fasting: albumin, ALT, AST, ALP, amylase, lipase, bicarbonate, bilirubin (total and direct), BUN (urea where BUN not tested), calcium, chloride, creatinine, gamma-glutamyl transferase (GGT) glucose, magnesium, myoglobin, phosphorus, potassium, sodium, total protein, and creatinine kinase (including CK-MM and CK-MB) and uric acid.

Assessment	Details
	Check-in eligibility will be determined by Day-1 on-site Total CK and CK-MB, not by Day -1 outside laboratory Total CK and isoenzymes. The estimated GFR will be calculated by the CKD-Epi method. Note: Post-dose or PM (afternoon or mid-day) samples are not required to be fasted.
Urinalysis	Urinalysis by dipstick; if results are abnormal, follow up with microscopy. Urine creatinine, protein, albumin, protein/creatine, albumin/creatinine, Kim-1, and sediment microscopy in MAD Cohort 3.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatinine kinase, CK-MB = creatinine kinase heart; CK-MM = creatinine kinase skeletal muscle; CrCL = creatinine clearance; CRU = clinical research unit; ECG = electrocardiogram; INR = International Normalized Ratio; PK = pharmacokinetic; PT = prothrombin time; QTcF = QT interval corrected for heart rate using Fridericia's formula; RBC = red blood cell; WBC = white blood cell.

8.3.1. Laboratory Assessments

See Table 8 for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Table 1, Table 2, and Table 3) for timing and frequency.

8.3.1.1. Reporting and Evaluation of Laboratory Test Results

Adverse events will be collected from the first dose of study medication, therefore the laboratory results from the pre-dose sample taken closest to dosing will be considered baseline. All laboratory test results must be reviewed for clinical significance by the Investigator. Laboratory test results outside the normal range (hematology, chemistry, urinalysis) that worsen in severity grade (see Section 8.4.4.3) from baseline and are deemed clinically significant by the Investigator should be reported as AEs. A new laboratory abnormality resulting in study drug interruption, dose reduction, treatment discontinuation, intervention, is symptomatic, requires treatment or otherwise has an impact on the subject should be reported as an AE, unless it is part of a clinical diagnosis reported as an AE.

All laboratory values outside the normal range are to be evaluated before the next dose of study drug.

8.3.1.2. Repeat Testing

Repeat testing of any clinically significant laboratory test will be performed until the value returns to within the normal range, returns to the baseline level, or clinically stabilizes.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

8.4.1. Definition of Adverse Event

AE Definition
Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

8.4.1.1. Events Meeting the Adverse Event Definition

Events Meeting the AE Definition
• Laboratory test results outside the normal range (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements), including any that worsen in severity grade (see Section 8.4.4.3) from baseline, which are considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition resulting in an increase in severity grade. • Condition detected or diagnosed that is new in onset or increased in severity grade from the baseline condition. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE.

8.4.1.2. Events NOT Meeting the Adverse Event Definition

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

8.4.2. Definition of Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that at any dose:

1. **Results in death**
   - Death due to disease progression or relapse is not considered an SAE unless the Investigator deems it possibly related to the study treatment.
2. **Is life-threatening**
   - The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
3. **Requires inpatient hospitalization or prolongation of existing hospitalization**
   - In general, hospitalization signifies that the participant has remained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
   - Hospitalization for preplanned procedure and/or study-related treatment or procedure that did not worsen from baseline is not considered an SAE.
   - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
4. **Results in persistent disability/incapacity**
   - Disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or per clinical judgment.
5. **Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child)**
6. **Other situations (Important medical events):**
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious (e.g., invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse).
   - Any other important medical event that based upon appropriate medical judgment may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above (e.g., may not result in death, be life-threatening, or require hospitalization).

8.4.3. Time Period for Collecting AE and SAE Information

All SAEs and AEs will be recorded from first dose of study medication (see Section 8.3.1.1 regarding laboratory-associated AE assessments).

If the Investigator becomes aware of an SAE any time after the Follow-up telephone call, the Sponsor should be notified immediately (i.e., within 24 hours). Report the SAE using the method described below Section 8.4.5.

8.4.4. Recording of Adverse Events and/or Serious Adverse Events

8.4.4.1. Terms of Reported Adverse Events

All AEs will be recorded in the eCRF, including start and stop dates, severity/grade, study drug relationship, and event outcome.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) should be documented as the AE.

8.4.4.2. Detection of Adverse Events and Serious Adverse Events

The Investigator will record all observed and reported AEs. In addition, each subject will be questioned with regard to AEs.

8.4.4.3. Severity of Adverse Events

Severity of AEs will be graded as:

- **Mild:** event may be noticeable to the subject; does not influence daily activities; usually does not require intervention
- **Moderate:** event may be of sufficient severity to make the subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- **Severe:** event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed

If the severity of an AE changes more than once a day, the maximum severity for the event should be listed. If the severity changes over a number of days, these mini-events or changes should be recorded separately (i.e., having distinct onset dates).

8.4.4.4. Causal Relationship with Study Treatment

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship. Investigators should use their knowledge of the subject's medical/disease history, the specific circumstances of the event, the mechanism and/or target of the study drug, and potential alternative causes to determine if an AE is considered related to the study drug:
  - Definitely: The event has a plausible time relationship to drug intake, cannot be explained by the disease under study or other drugs, or has a definitive pharmacologic relationship to the study drug.
  - Probably: The event has a reasonable time relationship to drug intake and is unlikely to be attributed to the disease under study or other drugs.
  - Possibly: The event has a reasonable time relationship to drug intake and could also be attributed to the disease under study or other drugs.
  - Not related: The event has a time relationship to drug intake that makes a relationship impossible, or is clearly attributable to the disease under study, to other drugs, or to other factors or events.
- The Investigator will consult the Investigator's Brochure (IB) in the assessment and will use clinical judgment in the determination.
- For each AE/SAE, the Investigator **must** document in the medical notes that the event has been reviewed and an assessment of causality provided.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data. The Investigator may change causality determination in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.4.4.5. Follow-up of Adverse Events

Adverse events should be followed until the AE has resolved, is resolving, returned to baseline, or stabilized; withdrawal of consent; or death.

8.4.5. Reporting of Serious Adverse Events (SAE)

The Sponsor or designee must be notified using an SAE Report form within 24 hours of the Investigator becoming aware of an SAE. This timeframe is also applicable to follow-up information for previously reported SAEs.

The Investigator is obligated to obtain supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The SAE Report form must be printed, signed, and emailed to:

Contact Email:	mtr601sae@motricbio.com
Sponsor Medical Monitor Contact Phone:	+1 (301) 706-4851

The SAE Report form must be retained in the site records. Follow-up information will be reported in the same method as above.

8.4.6. Reporting of Deaths

Death must be reported if it occurs during the SAE reporting period as noted in Section 8.4.3.

8.4.7. Adverse Events of Special Interest (AESIs)

The myosin-2 isoform present in fast-twitch skeletal muscles and the extra-ocular muscles could be affected by MTR-601. Oculofacial AEs or any reduction in movement of the eyes, with potential for disconjugate gaze and "dizziness" or "imbalance" will be noted as an AESI. Additionally, AEs relating to swallowing or proximal muscle weakness (evaluated as part of the routine neurological examination) will be noted as an AESI. AEs related to reductions in eGFR, reductions in urinary output and/or urinary retention (via IPSS and Ultrasound) will be noted as an AESI.

8.4.8. Pregnancy

Details of all pregnancies in female subjects or in female partners of male subjects (after appropriate consent for use of medical information has been obtained) will be reported to the Sponsor or designee at the email noted in Section 8.4.5 within 24 hours of the Investigator's awareness.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The subject/pregnant female partner will be followed to determine the outcome of the pregnancy.

The Investigator will collect follow-up information on the subject/pregnant female partner and the neonate, and forward to the Sponsor or designee.

Any female subject who becomes pregnant while participating in the study will discontinue study drug.

8.4.9. Overdose

Refer to Section 6.7 for information regarding MTR-601 overdose.

8.5. Pharmacokinetics

The concentrations and calculated PK parameters of MTR-601 and accumulation of MTR-601 in muscle (from biopsy) will be assessed based on blood, urine, and tissue samples collected from subjects during the study. Potential MTR-601 metabolites may also be evaluated in blood and

urine. Collection time points for the assessment of pharmacokinetics are detailed in the Schedule of Assessments (Table 1, Table 2, and Table 3). Additional details regarding sample collection will be included in a separate Laboratory Manual.

Biopsy samples will be collected using a Bard Magnum 12 gauge or functionally similar spring-loaded sampling device potentially requiring at most 2 biopsy samplings to achieve a goal of 20 to 40 mg of tissue per biopsy time point.

8.6. Genetics

Buccal Samples will be collected for potential analysis of genetic and/or protein endpoints, including CYP genotyping. These samples will be retained for 5 years, after which they will be destroyed. Collection time points for the assessment of genetic sampling are detailed in the Schedule of Assessments (Table 1, Table 2, and Table 3). Additional details regarding sample collection will be included in a separate Laboratory Manual.

8.7. Pharmacodynamics – Biomarkers and Body Muscle Mass Assessment

Blood samples for biomarker analysis will be collected as detailed in the Schedule of Assessments (Table 1, Table 2, and Table 3).

An estimate of body muscle mass will be determined by body measurements (waist, chest, neck circumference) and with bioimpedance measurements.

Additional details regarding sample collection will be included in a separate Laboratory Manual.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal statistical hypotheses testing will be performed.

9.2. Sample Size Determination

This is a single center study conducted at 1 site and will enroll up to approximately 88 subjects.

This sample size accommodates withdrawal of consent or replacement for other non-TEAE reasons and is appropriate for dose escalation studies of this nature.

9.3. Analysis Populations

For the purposes of analysis, the following populations are defined in Table 9.

Table 9: Definitions of Analysis Populations

Analysis Population	Definition
Safety	Includes all subjects who received at least one dose of MTR-601 or placebo. This is the primary population for exposure and safety analyses.
Pharmacodynamic	Includes all subjects who received at least one dose of MTR-601 or placebo and have at least one post-baseline pharmacodynamic assessment. This is the primary population for pharmacodynamic endpoints.
Pharmacokinetic	Includes all subjects who received study treatment and have MTR-601 or placebo plasma concentration data. All such subjects will be evaluated for PK unless major protocol deviations may have affected the data or if key dosing information is missing. This is the primary population for PK analysis.

9.4. Statistical Analyses

This is a non-powered, dose-finding study. Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum, and maximum. In addition, changes from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. No interim analyses are planned.

9.5. Safety and Tolerability

Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables.

9.5.1. Pharmacokinetics

Individual plasma concentrations, amounts excreted in urine, concentrations in plasma and derived PK parameters will be listed individually, displayed in appropriate graphics, and summarized using descriptive statistics (including arithmetic mean, standard deviation [STD], geometric mean, median, minimum, maximum, and percent coefficient of variation [CV%]).

9.5.2. Pharmacodynamics

Pharmacodynamic effects will be explored, including effects on muscle strength as a function of dose, exposure, muscle accumulation (with potential adjustments for total body muscle mass/composition).

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Protocol Compliance/Deviations

The Investigator agrees to conduct the study in compliance with the protocol and all amendments. Any protocol deviation(s) should be recorded in the source documents along with a clear description of the deviation(s) and cause.

10.2. Study Termination

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB); issues with study drug; or at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- Dose escalation is halted, and no intermediate doses are proposed
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects
- Cancellation of the drug development program

The Sponsor may suspend dosing or terminate the study at any time for any reason. The Sponsor will notify the Investigator if the study is prematurely terminated. The Investigator must promptly contact all subjects to arrange final study visit(s) and procedures, as directed by the Sponsor.

10.3. Case Report Forms

An electronic case report form (eCRF) is required for each enrolled subject. For screen failure subjects, a minimal set of data will be collected as noted in Section 5.4. Data entered in the eCRF must be consistent with the source documents.

The Investigator has ultimate responsibility for the collection and reporting of all data entered in the eCRF and any other data collection forms and will be electronically signed by the Investigator to attest that the data contained in the eCRF are accurate.

10.4. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents (e.g., hospital records, patient hard copy/electronic files, clinical/office charts, pharmacy dispensing records, X-rays) are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is

being conducted in accordance with the currently approved protocol and any other study agreements, International Council for Harmonisation Good Clinical Practice guideline E6 (ICH GCP), and all applicable regulatory requirements.

10.5. Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for the data to be used as described in the informed consent form (ICF).

The subject must also be informed that medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.6. Recordkeeping

The Investigator agrees to keep and maintain records that would permit the Sponsor and regulatory authorities to evaluate/audit the study. These include the identity of subjects, IRB correspondence, original signed ICFs, source documents, the eCRFs, SAE/Pregnancy Report forms, drug storage/accountability/disposition records, and correspondence (e.g., letters, email, meeting minutes, telephone call records) with the Sponsor or designee. Records should be retained by the Investigator for a minimum of 15 years after completion or discontinuation of the study, according to the ICH guidelines, local regulations, or as specified in the clinical study agreement, whichever is longer.

If the Investigator becomes unable to retain study records for any reason (e.g., retirement, relocation), they must be transferred to the Sponsor or to a designee acceptable to the Sponsor (e.g., another investigator, another institution, or independent third party).

10.7. Quality Control and Quality Assurance

The Sponsor or designee will conduct periodic site visits or audits during or after the study to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors may review the drug storage area, study drug stocks, drug storage/accountability/disposition records, source documents, and regulatory documentation. The Investigator and institution will permit direct access to the physical spaces, records, and source documents to perform this verification to the Sponsor or designee monitors/auditors, IRB members, and appropriate regulatory authority inspectors.

The Investigator must immediately notify the Sponsor or its designee of any regulatory authority inspection notification, will cooperate with the Sponsor or designee to prepare the study site

for the inspection, will be present during the inspection along with relevant study staff, will allow the Sponsor or designee to be present during the inspection, and will provide copies of any inspection findings.

10.8. Financial Disclosure

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

11. ETHICS

11.1. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH GCP Guidelines, and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, ICH GCP, and applicable local regulatory requirements and laws.

11.2. Written Informed Consent

An informed consent form (ICF) meeting the requirements of 21 CFR §50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable), must be reviewed and approved by the Sponsor, approved by the IRB before use, and available for inspection.

The Investigator or authorized representative will explain the nature of the study to the subject and answer all questions regarding the study. Subjects must be informed that their participation is voluntary, and if they choose to participate, will be required to sign the approved ICF. The medical record must include a statement that written informed consent was obtained before any study procedures were performed, along with the date written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. The original signed ICF will be retained in the Investigator's records, with a copy provided to the subject.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

11.3. Institutional Review Board/Independent Ethics Committee

The protocol, protocol amendments, ICF, Investigator's Brochure (IB), and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects. Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will provide written summaries of the status of the study and any other significant safety findings to the IRB annually or more frequently in accordance with its requirements, policies, and procedures. At the end of the study, the Investigator will notify the IRB of the conclusion of the study and its outcome.

12. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13. REFERENCES

1. Chang, E., et al., *A Review of Spasticity Treatments: Pharmacological and Interventional Approaches.* Crit Rev Phys Rehabil Med, 2013. **25**(1-2): p. 11-22.
2. Careta, M.F., L. Delgado, and R. Patriota, *Report of Allergic Reaction After Application of Botulinum Toxin.* Aesthet Surg J, 2015. **35**(5): p. NP102-5.
3. Pavone, V., et al., *Botulinum Toxin Treatment for Limb Spasticity in Childhood Cerebral Palsy.* Front Pharmacol, 2016. **7**: p. 29.
4. Gyimesi, M., et al., *Single Residue Variation in Skeletal Muscle Myosin Enables Direct and Selective Drug Targeting for Spasticity and Muscle Stiffness.* Cell, 2020. **183**(2): p. 335-346 e13.
5. Graham, B.L., et al., *Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement.* Am J Respir Crit Care Med, 2019. **200**(8): p. e70-e88.