Statistical Analysis Plan

Title: A Randomized, Double-Blind, Placebo-Controlled, First-in-Human, Single and Multiple Ascending Dose Study of MTR-601 in Healthy Volunteers

Protocol Number: MTR-601-NHV-101

Protocol Version: Version 4.0/Date 15-April-2024

SAP Version: Final version 1.0, Date 18-Jun-2024

SAP Authors: Murli Manohar Sharma, M.Sc. Statistics

Kathryn Roupe, PhD

Previous SAP Versions

Not Applicable

SAP Amendments before database lock

Version	Issue Date	Section	Revision / Addition	Rationale

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Definition
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
eGFR	Glomerular filtration rate
EMA	European medicines agency
FEV_1	Forced expiratory volume in one second
FIH	First-in-human
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase

Abbreviation	Definition
HED	Human equivalent dose
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
INR	International normalized ratio
IP	Investigational product
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
PFT	Pulmonary Function Test
PI	Principal investigator
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
SAP	Statistical Analysis Plan

Abbreviation	Definition
SAS	Statistical Analysis System
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
ULN	Upper limit of normal

1 INTRODUCTION

This document details the planned statistical analyses for Motric Bio, protocol "MTR-601-NHV-101" study titled "A Randomized, Double-Blind, Placebo-Controlled, First-in-Human, Single and Multiple Ascending Dose Study of MTR-601 in Healthy Volunteers".

The proposed analyses are based on the contents of the final version 4.0 of the protocol (dated 15-Apr-2024). Exploratory parameters/endpoints will be documented separately in standalone report.

This is a phase 1, randomized, double blind, placebo-controlled, FIH (first in human) 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 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.

The total sample size will be up to 88 subjects to accommodate withdrawal of consent or replacement for other non-TEAE reasons.

SAD/MAD Dose Level Cohorts

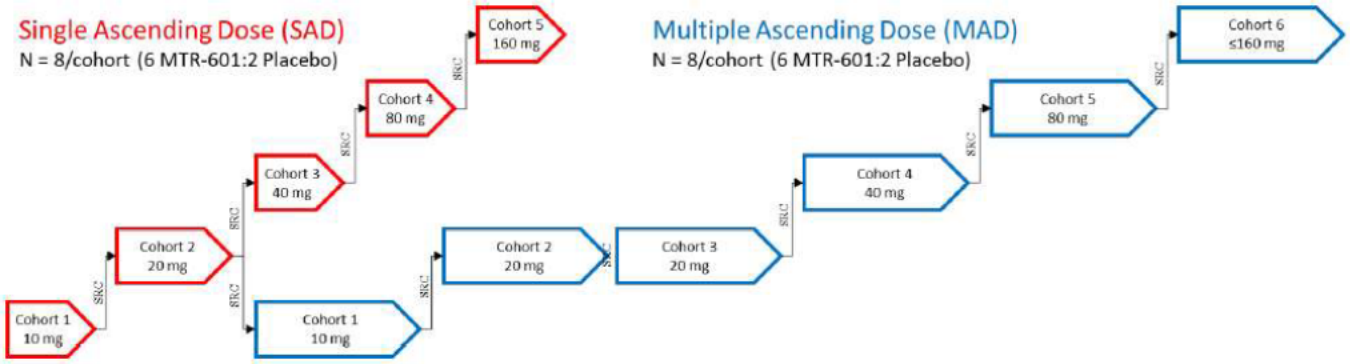
SAD/MAD Dose Level Cohorts [a]				
SAD/MAD Cohort [a & b]	**Dose [g]**	**Fasted**	**Fed Standard [c]**	**N [e]**
SAD Level 1	10 mg		✓	8 [f]
SAD Level 2, Two-Dose [d]	20 mg	✓	✓	8 [f]
SAD Level 3	40 mg		✓	8 [f]
SAD Level 4	80 mg		✓	8 [f]
SAD Level 5	160 mg		✓	8
MAD Level 1	10 mg		✓	8
MAD Level 2	20 mg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

Study schema for SAD and MAD as follows:



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.

2 STUDY 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 Ultrasonography
Secondary	
To evaluate the plasma and urine pharmacokinetics (PK) of MTR-601 [redacted]	Pharmacokinetic evaluations MAY include: • Concentration-time relationships • Estimations of dose proportionality at steady state • Estimation of time to achieve steady state based on qualitative evaluation of mean predose concentrations. • PK evaluation of potential MRT-601 metabolites may also be included at the time of analysis [redacted]

3 SAMPLE SIZE

This is a single canter 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.

4 RANDOMIZATION

SAD cohorts:

- For each cohort (Level 1-5), 6 subjects will be randomized to receive MTR-601 and 2 subjects will be randomized to receive placebo.
- The SAD cohorts will be randomized 1:1 for sentinels and remaining 6 subjects in each cohort will be randomized 5:1 to receive MTR-601 or placebo. 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.

In addition to the randomization scheme, there are also some specific instructions for the SAD Level 2, Two-Dose level cohort:

- For the first dose, subjects will be fasting.
- For the second dose, subjects will be fed state (standard not-high fat breakfast) 30 minutes before dosing.

MAD cohorts:

- For each cohort (Level 1-6), 6 subjects will be randomized to receive MTR-601 and 2 subjects will be randomized to receive placebo.

There are no sentinels in the MAD cohorts.

Cohort Type	Sentinels	Remaining Subjects
SAD	1:1	5:1
MAD	0	6:2

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.

5 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) must be approved prior to database lock / breaking of the blind for analysis. If post database lock, additional statistical analyses or changes to the statistical analysis are required, then those will be documented in a Post Database Lock Statistical Analysis Plan Addendum.

5.1 Analysis Population

The following populations are defined for the purposes of analysis.

5.1.1 Enrolled Population

The Enrolled Set includes all subjects screened / who gave informed consent.

5.1.2 Safety Population

Includes all subjects who received at least one dose of MTR-601 or placebo. This is the primary population for exposure and safety analyses.

5.1.3 Pharmacodynamic Population

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.

5.1.4 Pharmacokinetic (PK) Population

Includes all subjects who received study treatment and have sufficient MTR-601 plasma concentration data to estimate at least one of the planned PK parameters. 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.

5.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

5.2.1 Age

Age in years at informed consent will be calculated using SAS function as

Age (years) = floor((intck('month',birthdate,date)-(day(date)<day(birthdate)))/12)

5.2.2 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labelled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

5.2.3 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

For Cohort level 2, variables that will be summarized by treatment, the baseline for each dosing period is defined as the last non-missing value (either scheduled, unscheduled or repeat) that is collected before dosing for the relevant dosing period.

5.2.4 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

5.2.5 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates for events occurring during study conduct. Historical dates such as dates of medical history or prior medications may be missing or partial. Dates (historical or during study conduct) will only be imputed if a full date is needed for a calculation or to support a definition.

All dates presented in the individual subject listings will be as recorded on the Electronic Case Report Form (eCRF).

5.2.5.1 Missing Adverse Events Dates

In the rare case that an Adverse Event (AE) start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken, and it will be assumed that the AE is treatment emergent and occurred after first dosing. If an adverse event stop date is missing it will be assumed that the AE is ongoing.

5.2.6 Exposure to Study Drug

Exposure to study drug will be calculated (in days) as follows from the date of last dosing minus the first day of dosing + 1.

5.2.7 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

5.2.8 Change from Baseline

Change from baseline in absolute terms is defined as the baseline value subtracted from the post-baseline value:

$$Change\ from\ Baseline\ =\ Post\text{-}baseline\ Value\ -\ Baseline\ Value$$

5.2.9 Electrocardiogram (ECG) Data

For ECG data recorded on continuous scales, if replicate / triplicate values are recorded at a time point, the mean or the replicates rounded to the nearest integer will be used for summarization. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

5.2.10 Columbia-Suicide Severity Rating Scale (C-SSRS)

The following outcomes are C-SSRS categories and have binary responses (yes / no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behaviour
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)

Category 10	Completed Suicide

Suicidal Ideation since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS.

Suicidal Behaviour since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal behaviour questions (categories 6-10) on the C-SSRS.

There will be no imputation of missing data for C-SSRS.

5.2.11 Unscheduled Visits

Only scheduled post-baseline laboratory and vital signs values will be tabulated unless otherwise stated. Post-baseline repeat / unscheduled assessments will be included in all listings in the relevant appendices to the CSR.

5.2.12 Pharmacokinetic Parameters

The following plasma PK parameters will be calculated for MRT-601 after single ascending doses (SAD):

Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time of the maximum plasma concentration
AUC_{0-24}	Area under the plasma concentration-time curve from time-zero to 24 h postdose
AUC_{last}	Area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{inf}	Area under the plasma concentration-time curve from time-zero extrapolated to infinity; calculated as: $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$ Note: Additional criteria for reporting AUC_{inf} are summarized in Section 5.14
AUC_{Extrap} (%)	Percentage of AUC_{inf} based on extrapolation; calculated as: $AUC_{Extrap} = 100 \times [1-(AUC_{last}/AUC_{inf})]$
λ_z (Lambda-z, k_{el})	Apparent elimination rate constant; calculated as the negative slope of the linear regression through the terminal log-linear segment of the plasma concentration-time curve Note: Additional criteria for reporting λ_z are summarized in Section 5.14

Parameter	Definition
$T_{1/2}$	Observed terminal elimination half-life; calculated as: $T_{1/2} = \ln(2)/\lambda_z$
CL/F	Apparent total body clearance after extravascular administration, calculated as: CL/F = Dose/AUC_{inf}, where F is the bioavailability
V_z/F	Apparent volume of distribution after extravascular administration, calculated as: V_z/F = Dose/($AUC_{inf} \times \lambda_z$), where F is the bioavailability
C_{last}	Last observed quantifiable plasma concentration
T_{last}	Time of the last observed quantifiable plasma concentration

The following plasma PK parameters will be calculated for MRT-601 after multiple ascending doses (MAD) for Day 1 and Day 7:

Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time of the maximum plasma concentration
AUC_{0-12} (AUC_{tau})	The area under the plasma concentration-time curve from time-zero to 12 hours postdose, calculated by the linear trapezoidal method (Cohorts 1 and 2)
AUC_{0-24} (AUC_{tau})	The area under the plasma concentration-time curve from time-zero to 24 hours postdose (24 h = dosing interval), calculated by the linear trapezoidal method (predose samples collected on Days 2 and 8 will be used as Day 1, 24 h and Day 7, 24 h samples for this calculation)

The following plasma PK parameters will be calculated for MRT-601 after multiple ascending doses (MAD) for Day 14:

Parameter	Definition
$C_{max,ss}$	Maximum observed plasma concentration
$T_{max,ss}$	Time of the maximum plasma concentration

Parameter	Definition
AUC_{tau}	The area under the plasma concentration-time curve over the 24 h dosing interval, calculated by the linear trapezoidal method
C_{avg}	Average plasma concentration over the 24 h dosing interval, calculated as: $C_{avg} = AUC_{tau}/tau$
C_{last}	Last quantifiable plasma concentration
T_{last}	Time of the last quantifiable plasma concentration
CL_{ss}/F	The apparent total clearance at steady-state after extravascular administration, calculated as: $CL_{ss}/F=Dose/AUC_{tau}$, where F is the bioavailability
V_z/F	The apparent volume of distribution at steady-state after extravascular administration, calculated as: $V_z/F=Dose/(AUC_{tau} \times \lambda_z)$, where F is the bioavailability
R_{AUC}	Accumulation ratio of AUC_{tau}, calculated as: AUC_{tau} (Day 14)/AUC_{0-24} (Day 1) for Cohorts 3 onward only
R_{Cmax}	Accumulation ratio of C_{max}, calculated as: C_{max} (Day 14)/ C_{max} (Day 1)

The following urine PK parameters will be calculated for MRT-601 (SAD, MAD, Day 1, 7, and 14):

Parameter	Definition

Cum_Ae	Cumulative amount of drug excreted in urine across each collection interval (0-4, 0-8, 0-12, etc) Calculated through 96 h for SAD and MAD Day 14 Calculated through 24 h for MAD Days 1 and 7
Total Ae	Total amount of drug excreted in urine over the entire collection interval (0-96 h) Calculated through 96 h for SAD and MAD Day 14 Calculated through 24 h for MAD Days 1 and 7
Fe	Fraction of dose excreted in urine for each collection interval, calculated as: Fe = Ae/dose administered Calculated through 96 h for SAD and MAD Day 14 Calculated through 24 h for MAD Days 1 and 7
Fe (%)	Percent of dose excreted in urine for each collection interval, calculated as: Fe% = Ae/dose administered × 100
Cum_Fe (%)	Cumulative percent of dose excreted in urine across each collection interval (0-4, 0-8, 0-12, etc) Calculated through 96 h for SAD and MAD Day 14 Calculated through 24 h for MAD Days 1 and 7
Total Fe (%)	Total percent of dose excreted in urine over the entire collection interval (0-96 h), calculated as: Total Fe% = Total Ae/dose administered x 100 Calculated through 96 h for SAD and MAD Day 14 Calculated through 24 h for MAD Days 1 and 7
CL_r	Renal clearance, calculated as: SAD: CL_r = Total Ae/AUC_{inf} MAD: CL_r = Ae_{0-24}/AUC_{tau} (Day 14 only)

5.2.13 Randomization Strata

Not Applicable

5.3 Conventions

All safety data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher[2].

Summaries will be presented by treatment cohort or overall.

Treatment labels will be displayed as follows: For SAD

Presentation 1: For on and/or after treatment summaries

			MTR-601		
Placebo (N=XX)	Cohort 1 10 mg (N=XX)	Cohort 2 20 mg (N=XX	Cohort 3 40 mg (N=XX)	Cohort 4 80 mg (N=XX)	Cohort 5 160 mg (N=XX)
		Fast	Fed		

Presentation 2: For prior treatment summaries/histories/disposition

			MTR-601		
Placebo (N=XX)	Cohort 1 10 mg (N=XX)	Cohort 2 20 mg (N=XX)	Cohort 3 40 mg (N=XX)	Cohort 4 80 mg (N=XX)	Cohort 5 160 mg (N=XX)

Overall columns are to be included within the table shells as appropriate. Dose levels in Cohorts may be changed from the values above during the conduct of the trial based on emerging safety and PK data.
For MAD:

			MTR-601			
Placebo (N=XX)	Cohort 1 10 mg (N=XX)	Cohort 2 20 mg (N=XX)	Cohort 3 20 mg (N=XX)	Cohort 4 40 mg (N=XX)	Cohort 5 80 mg (N=XX)	Cohort 6 ≤160 mg (N=XX)

The placebo participants from all cohorts in each study stage will be pooled into a single placebo (per SAD or MAD) for all summaries and presentations.
Listings will be sorted in the following order Cohort treatment, subject, parameter, and visit unless otherwise stated. All data will be listed, subjects who were not randomized will be displayed after the randomized treatment.

The 'Screening Number' will be used and represented as 'Subject Number' for all TLFs.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of subjects in the column header unless otherwise specified in the footnote. For each

variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Means, medians and percentiles will be displayed to one more decimal place than the data, dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

Derived data where it is known in advance the result will be an integer for example number of days, or study day, will be presented with zero decimal places.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.3.4 or higher)[1] or SAS (Version 9.4 or higher)[2]. PK tables, listings, and figures will be created in WinNonlin and exported in Microsoft Word. Statistical analysis output will be created in SAS. PK concentration data will be summarized by treatment (dose level) at each nominal sample time or collection interval for SAD and by treatment (dose level) and study day at each nominal sample time or collection interval for MAD. PK parameter data will be summarized by treatment (dose level) for SAD and by treatment (dose level) and study day for MAD.

PK data (concentration-time data in all matrices) will be summarized by the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%), geometric mean, and geometric CV%. PK parameter data will be summarized by n, mean, SD, median, min, max, CV%, geometric mean, and geometric mean CV%. Individual concentrations and PK parameter values will be reported to 3 significant figures. For summary statistics, n will be reported as a whole number; mean, SD, median, min, max, CV%, geometric mean, and geometric mean CV% will be reported to 3 significant figures.

P- Values will be quoted to 4 decimal places consistent with SAS PVALUE*w.d* format set to PVALUE6.4. P-values < 0.0001 will be presented as p<0.0001.

5.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects who failed screening and the reasons for failure will be tabulated for all screened subjects.
- The number of subjects, who entered the study, were randomized and who are in each population, those who completed will be summarized by treatment cohort and overall, for all enrolled population.

- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment cohort and overall, for the safety population.

Subjects excluded from the analysis populations and the reason for their exclusion will be summarized and listed.

5.5 Protocol Deviations

Protocol deviations will be summarized for Safety population by classification (Minor/Major). A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

5.6 Baseline Comparability

The comparability of treatment cohort with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed. The Safety Population will be used to summarize all baseline and demographic data.

Standard continuous or categorical variable summaries will be presented by randomized treatment cohort for the following variables based on the Safety Analysis Set.

- Demographic data
- Medical history

5.7 Demographic Data

- Age at Informed Consent (years)
- Gender
- Race, where more than one race is selected the participant will be presented under the 'Multiple races' category in the summary but each selected race will be identified in the listing.
- Ethnicity
- Height at Screening (cm)
- Weight at Screening (kg)
- BMI at Screening (kg/m2)

5.8 Medical History

Separate tabulations of previous and ongoing conditions at screening will be presented by randomized treatment cohort and overall, for the Safety Population. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term.

5.9 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by randomized treatment cohort and overall, for the Safety Population. Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Concomitant medications will be summarized using Anatomic Therapeutic Chemical (ATC) Level 2. Prior and concomitant medications will be coded according to the most current version of WHO Drug Dictionary available at study start.

5.10 Substance Use

The details of the substance use will be collected at Screening and listing will be listed by each subject for Safety Population.

5.11 Exposure to Study Drug

All dosing will be listed for Safety Population.

5.12 Treatment Compliance

Not applicable.

5.13 Efficacy Analyses

Not Applicable.

5.14 Pharmacokinetic Analyses

5.14.1 Concentration-Time Data

5.14.1.1 Plasma

MRT-601 plasma concentration-time data will be tabulated by nominal time and treatment (dose level) for SAD and by nominal time, treatment (dose level), and study day for MAD using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero. Nominal and relative time will be presented in hours.

MRT-601 samples will be collected at:

SAD: 0 (pre-dose) and at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours post-dose.

SAD (2 dose, food effect): 0 (pre-dose 1) and at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours postdose

MAD, Day 1: 0 (predose) and at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, and 12 hours postdose for Cohorts 1 and 2. A 24 hour sample (Day 2, predose) was added for Cohort 3 onward.

MAD Day 7: 0 (predose) and at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, and 12 hours postdose for Cohorts 1 and 2. A 24 hour sample (Day 8, predose) was added for Cohort 3 onward.

MAD Day 14: 0 (pre-dose) and at 0.25, 0.50, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours post-dose.

Mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales using nominal times. Individual subject concentration-time data will be presented graphically on linear and semi-logarithmic scales using actual times. For individual subject concentration-time data, spaghetti plots (all subjects in one plot per treatment) and all treatments in one plot for each subject will be created.

For SAD, mean profiles and spaghetti plots will be created.

For SAD (food effect): mean profiles, spaghetti plots, and individual plots (fed vs. fasted) will be created.

For MAD: mean profiles comparing doses on Days 1, 7, and 14, mean profiles comparing study days per dose level, spaghetti plots (by dose level and study day), and individual plots comparing study days for each subject will be created.

The PK Population will be used in the tabulation of concentration-time data and in the creation of concentration-time profiles. The Safety Population will be used for the concentration-time listings.

5.14.1.2 Urine

MRT-601 concentration-time data in urine will be tabulated by dose level, study day, and collection interval using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantification (BLQ) will be set to zero.

Urine collection times are:

SAD: 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 (Day 2); from 48–72 hours post-dose (Day 3); and from 72–96 hours post-dose (Day 4).

MAD (Day 1): from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, 8–12 hours and 12–24 hours post-dose.

MAD (Day 7): from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, 8–12 hours, and 12–24 hours post dose

MAD (Day 14): from a pre-dose void and post-dose from 0–4 hours, 4–8 hours, 8–12 hours, 12–24 hours, 24–48 hours, 48–72 hours, and 72–96 hours post dose.

5.14.2 Pharmacokinetic Methodology

Concentration-time data for MRT-601 in plasma will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.3.4 or higher, Certara, L.P.)[2] in conjunction with Certara Integral™ (Version 23.10.1, Certara, USA, Inc.)[3]. The PK Population will be used in the PK analysis.

During the PK analysis, concentrations below the limit of quantification (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing". Calculation of the PK characteristics will be based on actual elapsed times [h] relative to dosing.

Lambda-z (λ_z) and AUC_{inf} Reporting Criteria

The following criteria will be used to report λ_z:

- At least three quantifiable concentrations will be used in the regression
- C_{max} or data prior to C_{max} will not be included in the regression.
- The adjusted regression coefficient (R^2 adj) should be ≥ 0.80.

If these acceptance criteria are not met, λ_z reported for individual subjects will be retained in PK parameter tables for informational purposes; λ_z will be excluded from summary statistics. Parameters calculated using λ_z ($T_{1/2}$, CL/F, V_z/F) will be reported as ND (not determinable). Lambda-z (λ_z) and descriptive parameters (λ_z time range, Adj R^2, etc.) will be presented in a separate listing.

If lambda-z acceptance criteria are met and AUC_{inf} is estimable, the following criteria are used to report AUC_{inf}:

- The percentage of AUC_{inf} based on extrapolation should be <30.0%.

If the percentage of AUC_{inf} based on extrapolation is 30.0% or greater, AUC_{inf} and AUC_{Extrap} will be retained in a PK parameter table for informational purposes; these parameters will be excluded from summary statistics, subsequent PK calculations (e.g., CL/F, and V_z/F), and statistical analysis (e.g., ANOVA).

At least 3 consecutive quantifiable concentrations are required to estimate AUC_{last}. If a PK profile has at least 1 quantifiable concentration, then C_{max}, and T_{max} will be reported; other parameters will be reported as missing (ND).

5.14.3 Statistical Analysis

5.14.3.1 Dose Proportionality

The pharmacokinetic parameters for C_{max}, AUC_{last}, and AUC_{inf} (SAD); C_{max} (MAD, Day 1 and Day 7); and $C_{max,ss}$ and AUC_{tau} (MAD, Day 14) will be compared across doses to assess dose proportionality (i.e., proportionality of a change in systemic exposure with a change in dose). Statistical analyses will be done using a power model (Smith, 2000)[4] of the following general form,

$$\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon,$$

Where

PK is the pharmacokinetic parameter tested (e.g. C_{max} or AUC)

$\ln(\beta_0)$ is the y-intercept,

β_1 is the slope (a value of $\beta_1 \approx 1$ indicates linearity), and

ε is an error term

The estimate of β_1 with the 90% CIs will be reported along with the associated p-value and the dose range for proportionality. Dose proportionality plots will be created as well.

5.14.3.2 Food Effect (SAD, 2 Dose)

As all treatments for SAD and MAD study parts are administered under fed conditions, a comparison of fasted and fed C_{max}, AUC_{last}, and AUC_{inf} will be performed.

Analyses of variance (ANOVA) will be performed on the natural log transformed AUC_{last}, AUC_{inf}, and C_{max} using MIXED procedure in SAS. The MIXED model will contain treatment as a fixed effect. The geometric mean ratios (Test (Fasted-Period 1)/Reference (Fed-Period 2)) and their 90% confidence intervals will be provided.

The Wilcoxon signed rank test will be used for a nonparametric comparison of T_{max} values; a significant difference is defined a priori as $p < 0.05$.

Conclusions regarding the results of the statistical analysis (ANOVA) of PK parameters across treatments will be based on the ratio of the geometric means (Test / Reference) and the 90% confidence interval about the ratio. No significant difference will be demonstrated if the 90% confidence intervals are fully contained within the limits of 80.00% to 125.00%.

5.15 Pharmacodynamic Analyses

The evaluation of PD parameter will be done following endpoints.

- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.16 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Population.

5.16.1 Adverse Events

AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA). The version of MedDRA to be used in this study will be defined in the data management plan (DMP).

Treatment emergent adverse events (TEAE) are reported according to protocol as any AE that has an onset on or after the dose of study drug or any pre-existing condition that has worsened on or after the first dose of study drug.

The following TEAE flag will be applied to distinguish AEs from TEAEs:

- Any AE that has a start date and time on or after the first dose of study drug

A treatment-related AE is defined as an AE as related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented for AEs incidence and/or number of events will be reported as appropriate:

- Overall summary of TEAEs
- TEAEs by system organ class and preferred term
- Treatment related TEAE by system organ class and preferred term
- Serious TEAE by system organ class and preferred term
- TEAE by system organ class, preferred term and maximum severity by system organ class, preferred term and relationship
- TEAEs leading to early withdrawal by system organ class and preferred term
- Adverse Events of Special Interest (AESIs) by system organ class and preferred term
- Listing of Serious TEAEs (presented in the Table section of the appendices).
- Listing of Deaths (presented in the Table section of the appendices).

Adverse event incidence is counted only once per system organ class and once per preferred term. The number and percent of subjects experiencing events are reported. Outputs reported at maximum severity show the highest severity reported by a patient per system organ class and preferred term.

In counting the number of AEs reported, a continuous event (i.e., reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

In the AE summary tables the system organ class will be order alphabetically and the preferred term within the system organ class will be order in decreasing frequency for the Overall column. In case of tie(s), the preferred term will be ordered alphabetically.

For SAD cohort 2 the AE will be attributed to the treatment as taken based on the event date and the dosing date.

All AEs will be listed for Safety population.

5.16.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment cohort and visit for each hematology, urinalysis, Coagulation, and serum chemistry parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each

follow-up visit and treatment cohort will be presented. All laboratory parameters will be listed in the order as per protocol (Table 8).

Laboratory tests will be reported in international system of units (SI) and will be used for analysis.

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented.

All other laboratory data including Pregnancy test (Urine or serum) or FSH, Urine drug screen for cotinine, alcohol and drugs of abuse, Serology data, liver function tests will be listed in the order as per protocol (Table 8 Safety Assessments).

5.16.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment cohort and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiration rate (breath / min)
- Body temperature (degrees Celsius)

All Vital Signs data, including details of any abnormalities, will be listed.

5.16.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated by treatment cohort and visit:

- Ventricular rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms)
- QTcB interval (ms) [Bazett's formula - QTcB]
- QTcF interval (ms) [Fridericia's formula - QTcF]

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to EOS/ET visit by treatment cohort will be presented.

All ECG data, including details of any abnormalities, will be listed.

5.16.5 Physical Examination

The body systems within the physical examination data at the end of the study will be summarized by treatment cohort (Normal; Abnormal NCS, Abnormal CS) as a shift from baseline table, by treatment and overall, for safety population.

All physical examination data, including any abnormalities, will be listed.

5.16.6 Neurological exam

The neurological Includes cranial nerve assessments II-XII, mental status, cerebellar function (finger to nose and gait), reflexes (bilateral bicep, patellar, and ankle), gross assessment of extremity strength, motor system, sensory system and gross assessment of proximal Muscle examination data at the end of the study will be summarized by treatment cohort (Normal; Abnormal NCS, Abnormal CS). Changes from baseline will also be tabulated. Details of clinically significant findings will be listed.

5.16.7 Spirometry Data

Descriptive statistics for observed values and changes from baseline in the following Spirometry variables will be tabulated by treatment cohort and visit:

- Forced expiratory volume in one second (FEV1)
- Forced vital capacity (FVC)
- FEV1/FVC ratio (FEV1 divided by FVC)

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to each follow-up visit will be presented.

All Spirometry data, including details of any abnormalities, will be listed.

5.16.8 Echocardiogram

Descriptive statistics for observed values and changes from baseline in the following Left Ventricular End-Diastolic Volume, Left Ventricular End-Systolic Volume and Left ventricular ejection fraction Echocardiogram variables will be tabulated by treatment cohort and visit:

- Left Ventricular End-Diastolic Volume (cm)

- Left Ventricular End-Systolic Volume (cm)
- Left Ventricular Ejection Fraction (%)

All Echocardiogram data will be listed.

5.16.9 Cardiac telemetry, and oximetry

All Cardiac telemetry, and oximetry data will be listed.

5.16.10 Body composition assessments

All Body mass composition assessments data (Fat Mass (kg), Fat Free Mass (kg), Muscle Mass (kg), Total Body Water Mass (kg), Bone Mass (kg), Basal Metabolic Rate (BMR) (kJ), BMI (kg/m^2) and Total Body Water (%) will be listed.

5.16.11 Muscle Biopsy

Descriptive statistics of the observed values will be presented by treatment cohort and visit for muscle biopsy data.

All Muscle Biopsy data will be listed.

5.16.12 Suicidal Ideation Questions

Responses to each the suicidal ideation of these questions at each applicable visit will be listed.

5.16.13 International-Prostate Symptom Score

The International-Prostate Symptom Score (I-PSS)[5] is based on the answers to seven questions concerning urinary symptoms. Each question is assigned points from 0 to 5 indicating increasing severity of the symptom. The total score can therefore range from 0 to 35.

Descriptive statistics for observed total score and changes from baseline will be tabulated by treatment cohort and visit.

All the I-PSS data listings will be presented for Safety Population.

5.16.14 Genetics

All Genetic biomarker (buccal swab) data will be listed.

5.16.15 PD Biomarker

Descriptive statistics of the observed values and change from baseline will be presented by treatment cohort and visit for each plasma PD biomarker.

All plasma biomarker data will be presented in by-subject listings. The listings will include normal range data, where available. Furthermore, a listing of out-of-range observations will be presented.

5.16.16 Renal function and Urinary tract evaluations

Descriptive statistics of the observed values and change from baseline will be presented by treatment cohort and visit for Cystatin C.

All Cystatin C and Urinary System Ultrasound data will be listed.

5.16.17 Contraception

All Contraception data will be listed.

5.16.18 Meal Consumption

All meal consumption data will be listed by subject.

6 INTERIM ANALYSIS

Unblinded review of data was conducted by the sponsor team.

7 SAFETY REVIEW COMMITTEE (SRC) ANALYSIS

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 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

In the event of an AE of such severity that required to identify the treatment administered, the investigator or SRC committee may request to break the blind of that subject only.

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 below Table.

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	≥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= millimetres 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 (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.

8 CHANGES TO PLANNED PROTOCOL ANALYSIS

There are no changes to the planned protocol analysis.

9 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. Phoenix™ WinNonlin® (Version 8.3.4 or higher, Certara, L.P.)
3. Certara Integral™ (Version 23.10.1 or higher, Certara, USA, Inc.
4. Smith et. al. (2000) Confidence Interval Criteria for Assessment of Dose Proportionality, Pharmaceutical Research Vol. 17, No. 10, 2000
5. I-PSS1_AU1.0_eng-USori

10 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures, and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Subject Disposition – SAD Enrolled Population	IP	
14.1.1.2	Subject Disposition – MAD Enrolled Population	IP	
14.1.1.3	Protocol Deviations - SAD Safety Population	IP	
14.1.1.4	Protocol Deviations - MAD Safety Population	IP	
14.1.2	**Demographics**		
14.1.2.1	Demographics and Baseline Characteristics - SAD Safety Population	IP	
14.1.2.2	Demographics and Baseline Characteristics - MAD Safety Population	IP	
14.1.3	**Baseline Characteristics**	IP	
14.1.3.1	Ongoing Medical History by System Organ Class and Preferred Term - SAD Safety Population	IP	
14.1.3.2	Ongoing Medical History by System Organ Class and Preferred Term - MAD Safety Population	IP	
14.1.3.3	Previous Medical History by System Organ Class and Preferred Term - MAD Safety Population	IP	
14.1.3.4	Previous Medical History by System Organ Class and Preferred Term - MAD Safety Population	IP	
14.1.3.5	Prior Medications by ATC Level 4 and Preferred Term - SAD Safety Population	IP	
14.1.3.6	Prior Medications by ATC Level 4 and Preferred Term - MAD Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.1.3.7	Concomitant Medications by ATC Level 4 and Preferred Term - SAD Safety Population	IP	
14.1.3.8	Concomitant Medications by ATC Level 4 and Preferred Term - MAD Safety Population	IP	
14.2	**Efficacy Data Not Applicable**		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Overall Summary of Adverse Events - SAD Safety Population	IP	
14.3.1.2	Overall Summary of Adverse Events - MAD Safety Population	IP	
14.3.1.3	Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term - SAD Safety Population	IP	
14.3.1.4	Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term - MAD Safety Population	IP	
14.3.1.5	Treatment-Related Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term - SAD Safety Population	IP	
14.3.1.6	Treatment-Related Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term - MAD Safety Population	IP	
14.3.1.7	Treatment-Emergent Serious Adverse Events (TESAEs) by Primary System Organ Class and Preferred Term - SAD Safety Population	IP	
14.3.1.8	Treatment-Emergent Serious Adverse Events (TESAEs) by Primary System Organ Class and Preferred Term - MAD Safety Population	IP	
14.3.1.9	Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term and Maximum severity - SAD Safety Population	IP	
14.3.1.10	Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term and Maximum severity - MAD Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.11	Treatment Related Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term and Maximum severity - SAD Safety Population	IP	
14.3.1.12	Treatment Related Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term and Maximum severity - MAD Safety Population	IP	
14.3.1.13	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Relationship - SAD Safety Population	IP	
14.3.1.14	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Relationship - MAD Safety Population	IP	
14.3.1.15	Treatment-Emergent Adverse Events Leading to Early Termination/Withdrawal by Primary System Organ Class and Preferred Term - SAD Safety Population	IP	
14.3.1.16	Treatment-Emergent Adverse Events Leading to Early Termination/Withdrawal by Primary System Organ Class and Preferred Term - MAD Safety Population	IP	
14.3.1.17	Treatment-Emergent Adverse Events of Special Interest by Primary System Organ Class and Preferred Term - SAD Safety Population	IP	
14.3.1.18	Treatment-Emergent Adverse Events of Special Interest by Primary System Organ Class and Preferred Term - MAD Safety Population	IP	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	Listing of Serious TEAEs - SAD Safety Population	IP	
14.3.2.2	Listing of Serious TEAEs - MAD Safety Population	IP	
14.3.2.3	Listing of Deaths - SAD Safety Population	IP	
14.3.2.4	Listing of Deaths - MAD Safety Population	IP	
14.3.2.5	Listing of TEAEs Leading to Study Withdrawal - SAD Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.2.6	Listing of TEAEs Leading to Study Withdrawal - MAD Safety Population	IP	
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Laboratory, Abnormal Values - SAD Safety Population	IP	
14.3.4.2	Laboratory, Abnormal Values - MAD Safety Population	IP	
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1	Vital Signs Data, Descriptive Statistics - SAD Safety Population	IP	
14.3.6.2	Vital Signs Data, Descriptive Statistics - MAD Safety Population	IP	
14.3.6.3	Physical Examination Data, Shift Summary - SAD Safety Population	IP	
14.3.6.4	Physical Examination Data, Shift Summary - MAD Safety Population	IP	
14.3.6.5	Neurological Examination Data, Shift Summary - SAD Safety Population	IP	
14.3.6.6	Neurological Examination Data, Shift Summary - MAD Safety Population	IP	
14.3.7	**Other Safety**		
14.3.7.1	Hematology Data, Descriptive Statistics - SAD Safety Population	IP	
14.3.7.2	Hematology Data, Descriptive Statistics - MAD Safety Population	IP	
14.3.7.3	Hematology Data, Normal Range Shifts from Baseline - SAD Safety Population	IP	
14.3.7.4	Hematology Data, Normal Range Shifts from Baseline - MAD Safety Population	IP	
14.3.7.5	Serum Chemistry Data, Descriptive Statistics - SAD Safety Population	IP	
14.3.7.6	Serum Chemistry Data, Descriptive Statistics - MAD Safety Population	IP	
14.3.7.7	Serum Chemistry Data, Normal Range Shifts from Baseline - SAD Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.8	Serum Chemistry Data, Normal Range Shifts from Baseline - MAD Safety Population	IP	
14.3.7.9	Coagulation Data, Descriptive Statistics - SAD Safety Population	IP	
14.3.7.10	Coagulation Data, Descriptive Statistics - MAD Safety Population	IP	
14.3.7.11	Coagulation Data, Normal Range Shifts from Baseline - SAD Safety Population	IP	
14.3.7.12	Coagulation Data, Normal Range Shifts from Baseline - MAD Safety Population	IP	
14.3.7.13	Urinalysis Data (Continuous), Descriptive Statistics - SAD Safety Population	IP	
14.3.7.14	Urinalysis Data (Continuous), Descriptive Statistics - MAD Safety Population	IP	
14.3.7.15	Urinalysis Data (Categorical), Descriptive Statistics - SAD Safety Population	IP	
14.3.7.16	Urinalysis Data (Categorical), Descriptive Statistics - MAD Safety Population	IP	
14.3.7.17	Urinalysis Data, Normal Range Shifts from Baseline - SAD Safety Population	IP	
14.3.7.18	Urinalysis Data, Normal Range Shifts from Baseline - MAD Safety Population	IP	
14.3.7.19	Cystatin C Data, Descriptive Statistics - SAD Safety Population	IP	
14.3.7.20	Cystatin C Data, Descriptive Statistics - MAD Safety Population	IP	
14.3.7.21	12 Lead ECG, Descriptive Statistics - SAD Safety Population	IP	
14.3.7.22	12 Lead ECG, Descriptive Statistics - MAD Safety Population	IP	
14.3.7.23	12-Lead ECG, (Overall Interpretation), Shift Summary - SAD Safety Population	IP	
14.3.7.24	12-Lead ECG, (Overall Interpretation), Shift Summary - MAD Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.8.1	Spirometry Data, Descriptive Statistics - SAD Safety Population	IP	
14.3.8.2	Spirometry Data, Descriptive Statistics - MAD Safety Population	IP	
14.3.8.3	Spirometry, Shift Summary - SAD Safety Population	IP	
14.3.8.4	Spirometry, Shift Summary - MAD Safety Population	IP	
14.3.8.5	Echocardiogram Data, Descriptive Statistics - SAD Safety Population	IP	
14.3.8.6	Echocardiogram Data, Descriptive Statistics - MAD Safety Population	IP	
14.3.8.7	International-Prostate Symptom Score (I-PSS), Descriptive Statistics – SAD Safety Population	IP	
14.3.8.8	International-Prostate Symptom Score (I-PSS), Descriptive Statistics – SAD Safety Population	IP	
14.4	**PK Tables**		
14.4.1.1	Descriptive Statistics for Concentration-Time Data of MRT-601 in Plasma after Single Ascending Doses of MRT-601 – PK Population	IP	
14.4.1.2	Descriptive Statistics for Concentration-Time Data of MRT-601 in Plasma after Multiple Ascending Doses of MRT-601– PK Population	IP	
14.4.2.1	Descriptive Statistics for Concentration-Time Data of MRT-601 in Urine after Single Ascending Doses of MRT-601 – PK Population	IP	
14.4.2.2	Descriptive Statistics for Concentration-Time Data of MRT-601 in Urine after Multiple Ascending Doses of MRT-601 – PK Population	IP	
14.4.3.1	Descriptive Statistics for Amount of Unchanged MRT-601 Excreted in Urine after Single Ascending Doses of MRT-601 - PK Population	IP	
14.4.3.2	Descriptive Statistics for Amount of Unchanged MRT-601 Excreted in Urine after Multiple Ascending Doses of MRT-601 - PK Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.4.4.1	Descriptive Statistics for Cumulative Amount of Unchanged MRT-601 Excreted in Urine after Single Ascending Doses of MRT-601 - PK Population	IP	
14.4.4.2	Descriptive Statistics for Cumulative Amount of Unchanged MRT-601 Excreted in Urine after Multiple Ascending Doses of MRT-601 - PK Population	IP	
14.4.5.1	Descriptive Statistics for Fraction of Dose Excreted in Urine after Single Ascending Doses of MRT-601 - PK Population	IP	
14.4.5.2	Descriptive Statistics for Fraction of Dose Excreted in Urine after Multiple Ascending Doses of MRT-601 - PK Population	IP	
14.4.6.1	Descriptive Statistics for Percent of Dose Excreted in Urine after Single Ascending Doses of MRT-601 - PK Population	IP	
14.4.6.2	Descriptive Statistics for Percent of Dose Excreted in Urine after Multiple Ascending Doses of MRT-601 - PK Population	IP	
14.4.7.1	Descriptive Statistics for Cumulative Percent of Dose Excreted in Urine after Single Ascending Doses of MRT-601 - PK Population	IP	
14.4.7.2	Descriptive Statistics for Cumulative Percent of Dose Excreted in Urine after Multiple Ascending Doses of MRT-601 - PK Population	IP	
14.4.8.1	Descriptive Statistics for Plasma PK Parameters of MRT-601 after Single Ascending Doses of MRT-601 - PK Population	IP	
14.4.8.2	Descriptive Statistics for Plasma PK Parameters of MRT-601 after Multiple Ascending Doses of MRT-601 on Day 1 - PK Population	IP	
14.4.8.3	Descriptive Statistics for Plasma PK Parameters of MRT-601 after Multiple Ascending Doses of MRT-601 on Day 7 - PK Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.4.8.4	Descriptive Statistics for Plasma PK Parameters of MRT-601 after Multiple Ascending Doses of MRT-601 on Day 14 - PK Population	IP	
14.4.9.1	Descriptive Statistics for Urine PK Parameters of MRT-601 after Single Ascending Doses of MRT-601 - PK Population	IP	
14.4.9.2	Descriptive Statistics for Urine PK Parameters of MRT-601 after Multiple Ascending Doses of MRT-601 - PK Population	IP	
14.4.10.1	Dose-Proportionality Assessment of MRT-601 in Plasma after Single Ascending Doses of MRT-601 – PK Population	MR	
14.4.10.2	Dose-Proportionality Assessment of MRT-601 in Plasma after Multiple Ascending Doses of MRT-601 on Day 1 – PK Population	MR	
14.4.10.3	Dose-Proportionality Assessment of MRT-601 in Plasma after Multiple Ascending Doses of MRT-601 on Day 7 – PK Population	MR	
14.4.10.4	Dose-Proportionality Assessment of MRT-601 in Plasma after Multiple Ascending Doses of MRT-601 on Day 14 – PK Population	MR	
14.4.11.1	Statistical Analysis of the Natural Log-Transformed PK Parameters of MRT-601 in Plasma after a Single Dose of 20 mg MRT-601 under Fasted (Test) and Fed (Reference) Conditions – PK Population	MR	
14.5	**PD Tables**		
14.5.1	Muscle Strength Data, Descriptive Statistics - SAD PD Population	IP	
14.5.2	Muscle Strength Data, Descriptive Statistics - MAD PD Population	IP	
14.5.3	Dynamometry and MicroFET 2 HHD Measurement Data, Shift Summary – SAD PD Population	IP	
14.5.4	Dynamometry and MicroFET 2 HHD Measurement Data, Shift Summary – MAD PD Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.5.5	Muscle Biopsy, Descriptive Statistics - SAD PD Population	IP	
14.5.6	Muscle Biopsy, Descriptive Statistics - MAD PD Population	IP	
14.5.7	Plasma (PD) Biomarker Data, Descriptive Statistics – SAD PD Population	IP	
14.5.8	Plasma (PD) Biomarker Data, Descriptive Statistics – MAD PD Population	IP	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.1.1	Mean Plasma Concentration-Time Profiles of MRT-601 after Single Ascending Doses of MRT-601 Administered under Standard Fed Conditions on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.1.2	Mean Plasma Concentration-Time Profiles of MRT-601 after a Single Dose of 20 mg MRT-601 Administered under Fasted and High-Fat Fed Conditions on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.1.3	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Ascending Doses of MRT-601 on Day 1 on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.1.4	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Ascending Doses of MRT-601 on Day 7 on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.1.5	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Ascending Doses of MRT-601 on Day 14 on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.1.6	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Doses of 10 mg MRT-601 on Day 1, Day 7, and Day 14 on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.1.7	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Doses of 20 mg MRT-601 on Day 1, Day 7, and Day 14 over the 24 h Dosing Interval on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.1.8	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Doses of 40 mg MRT-601 on Day 1, Day 7, and Day 14 over	MR	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
	the 24 h Dosing Interval on Linear and Semi-logarithmic Scales- PK Population		
14.4.1.9	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Doses of 60 mg MRT-601 on Day 1, Day 7, and Day 14 over the 24 h Dosing Interval on Linear and Semi-logarithmic Scales - PK Population	MR	
14.4.1.10	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Doses of 80 mg MRT-601 on Day 1, Day 7, and Day 14 over the 24 h Dosing Interval on Linear and Semi-logarithmic Scales - PK Population	MR	
14.4.1.11	Mean Plasma Concentration-Time Profiles of MRT-601 after Multiple Doses of 160 mg MRT-601 on Day 1, Day 7, and Day 14 over the 24 h Dosing Interval on Linear and Semi-logarithmic Scales - PK Population	MR	
14.4.2.1	All Subject Plasma Concentration-Time Profiles of MRT-601 after Single Ascending Doses of MRT-601 on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.2.2	All Subject Plasma Concentration-Time Profiles of MRT-601 after Multiple Ascending Doses of MRT-601 on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.3.1	Individual Subject Plasma Concentration-Time Profiles of MRT-601 after a Single Dose of 20 mg MRT-601 (Cohort 2) under Fasted (Period 1) and High-Fat Fed (Period 2) Conditions on Linear and Semi-logarithmic Scales- PK Population	MR	
14.4.3.2	Individual Subject Plasma Concentration-Time Profiles of MRT-601 after Multiple Ascending Doses of MRT-601 on Days 1, 7, and 14 on Linear and Semi-logarithmic Scales- PK Population	MR	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.4.1	Assessment of MRT-601 C_{max} vs. Dose after Single Ascending Doses of MRT-601 – PK Population	MR	
14.4.4.2	Assessment of MRT-601 AUC_{last} vs. Dose after Single Ascending Doses of MRT-601 – PK Population	MR	
14.4.4.3	Assessment of MRT-601 AUC_{inf} vs. Dose after Single Ascending Doses of MRT-601 – PK Population	MR	
14.4.4.4	Assessment of MRT-601 $C_{max,ss}$ vs. Dose after Multiple Ascending Doses of MRT-601 on Day 1 – PK Population	MR	
14.4.4.5	Assessment of MRT-601 $C_{max,ss}$ vs. Dose after Multiple Ascending Doses of MRT-601 on Day 7 – PK Population	MR	
14.4.4.6	Assessment of MRT-601 $C_{max,ss}$ vs. Dose after Multiple Ascending Doses of MRT-601 on Day 14 – PK Population	MR	
14.4.4.7	Assessment of MRT-601 AUC_{tau} vs. Dose after Multiple Ascending Doses of MRT-601 on Day 14 – PK Population	MR	
14.4.5.1	Plasma Concentration-Time Profiles for MRT-601 after Single Ascending Doses of MRT-601 with Linear Regression for Estimating the Terminal Elimination Rate – PK Population	MR	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition - All Enrolled Population	IP	
16.2.1.2	Screen Failure - All Screened Subjects	IP	
16.2.1.3	Eligibility Criteria- All Screened Subjects	IP	
16.2.1.4	Populations - Enrolled Population	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations - Safety Population	IP	
16.2.4	**Demographic Data**		
16.2.4.1	Demographic and Baseline Characteristics- Safety Population	IP	
16.2.4.2	Previous and Ongoing Medical History - Safety Population	IP	
16.2.4.3	Substance Use - Safety Population	IP	
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	Study Medication Administration - Safety Population	IP	
16.2.5.2	Prior and Concomitant Medications - Safety Population	IP	
16.2.6	**PK Data**		
16.2.6.1	MRT-601 Plasma Concentration Listing by Subject (SAD) – Safety Population	MR	
16.2.6.2	MRT-601 Plasma Concentration Listing by Subject (MAD) – Safety Population	MR	
16.2.6.3	MRT-601 Urine Concentrations, Volume, Ae, Fe, and Fe% Listing by Subject (SAD) – PK Population	MR	
16.2.6.4	MRT-601 Urine Concentrations, Volume, Ae, Fe, and Fe% Listing by Subject (MAD) – PK Population	MR	
16.2.6.5	Terminal Elimination Rate for MRT-601 for Individual Subjects (SAD) – PK Population	MR	
16.2.6.6	PK Output Text (SAD) - Plasma	MR	
16.2.6.7	PK Output Text (MAD) - Plasma	MR	
16.2.6.8	PK Output Text (SAD) - Urine	MR	
16.2.6.9	PK Output Text (MAD) - Urine	MR	
16.2.6.10	SAS Output Text – Dose Proportionality Assessment (SAD)	MR	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.6.11	SAS Output Text – Dose Proportionality Assessment (MAD)	MR	
16.2.6.12	SAS Output Text – Food Effect Assessment	MR	
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data - Safety Population	IP	
16.2.7.2	Serious Adverse Event Data- Safety Population	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology Data - Safety Population	IP	
16.2.8.2	Serum Chemistry Data - Safety Population	IP	
16.2.8.3	Urinalysis Data - Safety Population	IP	
16.2.8.4	Coagulation Data - Safety Population	IP	
16.2.8.5	Cystatin C Data - Safety Population		
16.2.8.6	Covid-19 Test Data - Safety Population	IP	
16.2.8.7	Serology Data - Safety Population	IP	
16.2.8.8	Pregnancy Test Data - Safety Population	IP	
16.2.8.9	FSH (Follicle Stimulating Hormone) Data - Safety Population	IP	
16.2.8.10	Urine Drug, Alcohol and Cotinine Screen Data - Safety Population	IP	
16.2.9.1	Vital Signs Data - Safety Population	IP	
16.2.9.2	Lead ECG Data - Safety Population	IP	
16.2.9.3	Lead ECG Data (Overall Interpretation) - Safety Population	IP	
16.2.9.4	Physical Examination Data - Safety Population	IP	
16.2.9.5	Neurological Examination Data - Safety Population	IP	
16.2.9.6	Cardiac Telemetry Collection Data - Safety Population	IP	
16.2.9.7	Oximetry Collection Data - Safety Population	IP	
16.2.9.8	Columbia Suicide Severity Rating Scale (C-SSRS) Data - Safety Population	IP	
16.2.9.9	Spirometry Data - Safety Population	IP	
16.2.9.10	Echocardiogram Data from Transthoracic Echocardiography - Safety Population	IP	
16.2.9.11	Body Composition Data - Safety Population	IP	
16.2.9.12	Muscle Biopsy Data - Safety Population	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.9.13	Peripheral Magnetic Stimulation (PMS) Data - Safety Population	IP	
16.2.9.14	Peripheral Magnetic Stimulation (PMS) Medical Questionnaire Data - Safety Population	IP	
16.2.9.15	International-Prostate Symptom Score (I-PSS) Data - Safety Population	IP	
16.2.9.16	Urinary System Ultrasound Data - Safety Population	IP	
16.2.9.17	Genetic biomarker (buccal swab) Data - Safety Population	IP	
16.2.9.18	Contraception Form - Safety Population	IP	
16.2.9.19	Meal Data - Safety Population	IP	
16.2.10.1	Plasma Biomarker (PD) - Safety Population	IP	
16.2.10.2	Dynamometry and MicroFET 2 HHD Measurement Data - PD Population	IP	