

Motric Bio, Inc.

MTR 601-201

***A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to
Assess the Safety, Tolerability and Efficacy of MTR-601, a Novel Oral
Treatment in Patients with Cervical Dystonia***

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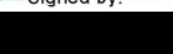
Statistical Analysis Plan

Version 2.0

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List of Abbreviations

Abbreviation	Description
ADL	Activities of daily living
AEs	Adverse events
AESI	Adverse events of special interest
ANCOVA	Analysis of Covariance
aPTT	Partial Thromboplastin Time
ATC2	Anatomical Therapeutic Chemical 2
BCRP	Breast Cancer Resistance Protein
BoNT	Botulinum Toxins
BLQ	Below Limit of Quantification
BMI	Body Mass Index
BUN	Blood urea nitrogen
CDQ-24	24-item Craniocervical dystonia questionnaire
CGI-C	Clinical Global Impression - Change
CGI-S	Clinical Global Impression - Severity
CI	Confidence Interval
CKD	Chronic Kidney Disease
ClinRO	Clinician-Reported Outcomes
CPK	Creatinine phosphokinase
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CYP3A	Cytochrome P450 3A
DBL	Database Lock
DSMB	Data Safety Monitoring Board
ECGs	Electrocardiograms
eCRF	Electronic Case Report Forms
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study
ESKD	End stage kidney disease
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
FU	Follow up
GGT	Gamma-glutamyl transpeptidase
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMPC	hydroxypropyl methylcellulose
ICF	Informed Consent Form

ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive response technology
LDS	Lactate dehydrogenase
LS	Least Square
MAR	Missing At Random
MATE1	Multidrug and Toxin Extrusion1
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
PE	Physical examination
PGI-C	Patient Global Impression - Change
PGI-S	Patient Global Impression - Severity
PK	Pharmacokinetics
PKS	Pharmacokinetics Analysis Set
PRO	Patient-Reported Outcomes
PT	Preferred term
QRS	Quantron Resonance System
QTcB	QT Interval corrected for heart rate using Bazett's formula
QTcF	QT Interval corrected for heart rate using Fridericia's formula
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Events
TEAEs	Treatment Emergent Adverse Events
TSQM	Treatment Satisfaction Questionnaire for Medication
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
WHO	World Health Organization

1. Introduction

As per International Conference on Harmonization (ICH) E9 [1] and ICH E9 (R1) [2], the main purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol and to include detailed procedures for executing the statistical analysis. This document outlines the statistical methods to be implemented in the analysis of the data collected within the scope of Motric Bio, Inc., Protocol MTR 601-201 (A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of MTR-601, a Novel Oral Treatment in Patients with Cervical Dystonia), Version 4.0[3] (04 Sep 2025).

Cervical dystonia (spasmodic torticollis) is the most common form of focal dystonia encountered in movement disorder clinics. It is a troublesome or even a debilitating movement disorder characterized by involuntary contractions of neck muscles, leading to abnormal head postures, tremors, and significant pain or discomfort [4]. This form of dystonia affects approximately 60,000 individuals in the United States alone, with a global impact of approximately 1 to 1.5 million individuals. Current therapies such as botulinum toxins (BoNT), baclofen (orally or intrathecally), dantrolene, and benzodiazepines are characterized by limited efficacy, multiple side effects, inconvenience, and pain to participants, and fail to address the issue systemically and offer sustained relief.

There are currently 5 BoNT products approved by the US FDA for the treatment of cervical dystonia, each with unique properties and potencies [5-7]. Although BoNT is currently considered the treatment of choice for cervical dystonia [8-10], some forms of dystonia do not respond well to BoNT, and loss of efficacy due to immuno-resistance continues to be a therapeutic challenge [11, 12]. Therefore, there is an important unmet need for other treatment options for patients with cervical dystonia.

MTR-601 is a novel, orally administered small molecule inhibitor of myosin-2 “fast” isoforms that selectively stabilizes the actin unbound conformation of myosin-2 isoforms that have a leucine at position 476 instead of a phenylalanine. This selectivity spares “slow” isoforms found in cardiac and smooth muscle and enables the efficient nervous system-independent relaxation of muscles, leading to relief of muscle-contraction related pain of participants. Preliminary findings from the first in human study suggest that MTR-601 may provide safe and tolerable symptom relief in cervical dystonia with oral administration. This novel muscle relaxant could be potentially used as a primary treatment in patients with

cervical dystonia or as an ancillary therapy in patients treated with BoNT who experience inadequate control or short duration response from the effects of BoNT. This study aims to evaluate the efficacy of MTR-601 in a larger, more diverse participant population with cervical dystonia.

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the primary, secondary, and exploratory study objectives.

2. Objectives

2.1. Primary Objectives

- To evaluate the safety and tolerability of MTR-601 in participants with cervical dystonia
- To evaluate the efficacy of MTR-601 in participants with cervical dystonia

2.2. Secondary Objectives

- To evaluate the plasma concentration of MTR-601 in participants with cervical dystonia
- To evaluate the effect of MTR-601 on other measures of efficacy

2.3. Exploratory Objectives

- To explore the effects of MTR-601 on measures of quality of life
- To explore the relationship between genotype and the clinical profile of MTR-601

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 2a, randomized, double-blind, placebo-controlled study of MTR 601-201 treatment in participants with cervical dystonia.

Up to 80 participants will be randomly assigned (ratio of 1:1) to receive either MTR-601 (80 mg during weeks 1-2 and 160 mg during weeks 3-4) or matching placebo. The investigator and the participant will be blinded to the assigned arm. Treatment will be administered via orange opaque capsules and matching placebo capsules.

The study will be divided into three periods: Screening, Treatment and Follow-up.

An initial screening period will take place during which preliminary eligibility of participants will be determined (between Day -90 and Day -1). If a participant is deemed to be eligible for the study, they will be instructed to not receive their next scheduled botulinum toxin treatment prior to entry into the study. A full Screening visit (V2) will occur between Day -16 and Day -1 to determine full study eligibility. Eligible participants will be scheduled to return to the clinic for randomization to study treatment and to receive the first dose of the Investigational Medicinal Product (IMP) (first exposure to treatment) (V3). This visit will be considered “Day 1” of the study.

Eligible individuals will present at the clinic on Day 1 for V3. At this visit, participants will be randomized into the study and receive the IMP, either MTR-601 or placebo. Participants will undergo other assessments as listed in Appendix 14.1. Participants will be provided with the IMP for the duration of the study and will be discharged home. Participants will take the first dose and subsequent doses of the IMP while at home qhs at bedtime. For the first two weeks (Days 1-14), individuals will take MTR-601 at 80 mg (or matching placebo) once daily (2 capsules of 40 mg), and for the second two weeks (Days 15-28), individuals will take MTR-601 at 160 mg (or matching placebo) once daily (4 capsules of 40 mg). At the end of the weeks 1 and 3 on Day 8 (V4), and Day 22 (V6) respectively, a telephone call or in-clinic visit will occur to check on the status of the participants. At the end of weeks 2 and 4 on Day 15 (V5) and Day 29 (V7) respectively, participants will return to the clinic for safety, efficacy (including TWSTRS) and pharmacokinetic evaluations.

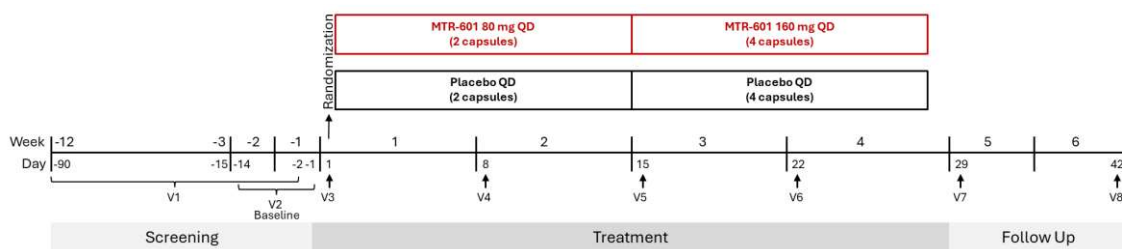
The participants will be followed up through 14 days after completion of treatment (on Day 28) to Day 42.

During the follow-up period, participants may resume treatment with botulinum toxin or daxibotulinum toxinA. Participants will return to the clinic 14 days after completion of treatment (Day 42) for the end of study visit (V8) where final safety assessments will be performed.

This study will evaluate the safety and efficacy of MTR-601 or placebo over a maximum of 6 weeks, 4 weeks of treatment and for an additional 2 weeks of follow-up. The primary objective will include evaluation of the safety, tolerability and efficacy of treatment of MTR-601 compared with placebo.

See the study Schema Figure 3-1 for a graphical representation of the study timeline.

Figure 3-1 Study Schema



3.2. Study Endpoints

3.2.1. Primary Endpoints

- Treatment-emergent Adverse Events (TEAEs).
- Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) overall score change from baseline at end of Week 4 (end of Treatment Period)

3.2.2. Secondary Endpoints

- Plasma MTR-601 concentrations on Day 14 and Day 28
- TWSTRS severity, pain and disability scores change from baseline at end of Week 4 (Treatment Period)
- TWSTRS overall and severity, pain, disability scores change from baseline at end of Week 2

3.2.3. Exploratory Endpoints

- CDQ-24 at end of Weeks 2 and 4
- TSQM at end of Weeks 2 and 4
- CGI-S and CGI-C at end of Weeks 2 and 4
- PGI-S and PGI-I at end of Weeks 1, 2, 3 and 4
- TWSTRS disability and pain at end of Weeks 1 and 3
- Selected endpoints to explore the relationship between genotype and the clinical profile of MTR-601 (Endpoints cannot be pre-defined but will be selected based on the clinical profile of MTR-601 in this study).

3.3. Study Estimands

In compliance with the ICH E9 (R1) guidelines [412], the estimands framework is used to provide the summary of estimands and transparency on the intercurrent event strategies that

are involved in the primary estimand definition. [Table 3-1](#) displays summary of the primary efficacy estimand and the strategies involved in managing the corresponding intercurrent events.

3.3.1. Primary Efficacy Estimand

The primary estimand is defined as the difference (MTR-601– placebo) of mean change from baseline in TWSTRS at the end of Week 4 in participants with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications. The difference of mean change from baseline in TWSTRS at the end of Week 4 is computed for all participants irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. In the event of a death, the difference of mean change from baseline in TWSTRS at the end of Week 4 will be calculated based on the available data while the participant was alive, with the last observed value prior to death carried forward for the analysis.

3.3.2. Supplementary Efficacy Estimand

The supplementary estimand in support of the primary objective is the difference (MTR-601– placebo) of mean change from baseline in TWSTRS at the end of Week 4 in participants with cervical dystonia as if there were no treatment discontinuation, dose modification, or use of prohibited concomitant medications. Observed data following these intercurrent events will be censored. The difference of mean change from baseline in TWSTRS at the end of Week 4 is computed for all participants irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. In the event of a death, the difference of mean change from baseline in TWSTRS at the end of Week 4 will be calculated based on the available data while the participant was alive, with the last observed value prior to death carried forward for the analysis.

Table 3-1 Summary of Primary and Supplementary Estimands and Strategies for Managing Intercurrent Events

Objective	Estimate the efficacy of MTR-601 in participants with cervical dystonia	
Estimand Label	Estimand 1a (Primary)	Estimand 1b (Supplementary)
Estimand Description	Difference (MTR-601–placebo) of mean change from baseline in TWSTRS at the end of Week 4 in patients with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications.	Difference (MTR-601–placebo) of mean change from baseline in TWSTRS at the end of Week 4 in patients with cervical dystonia as if there were no treatment discontinuation, dose modification, or use of prohibited concomitant medications.
Target Population	Patients aged ≥ 18 to ≤ 80 years with a confirmed clinical diagnosis of cervical dystonia	Patients aged ≥ 18 to ≤ 80 years with a confirmed clinical diagnosis of cervical dystonia
Endpoint	Change from baseline in TWSTRS at the end of Week 4	Change from baseline in TWSTRS at the end of Week 4
Treatment Condition(s)	Test: MTR-601 Reference: placebo	Test: MTR-601 Reference: placebo
Population-Level Summary	Difference (MTR-601–placebo) in the mean change from baseline at the end of Week 4	Difference (MTR-601–placebo) in the mean change from baseline at the end of Week 4
Intercurrent Event Strategy		
1. Death	While alive	While alive

Objective	Estimate the efficacy of MTR-601 in participants with cervical dystonia	
Estimand Label	Estimand 1a (Primary)	Estimand 1b (Supplementary)
2. Discontinuation of Treatment	Treatment policy	Hypothetical
3. Dose Modification	Treatment policy	Hypothetical
4. Prohibited Concomitant Medication¹	Treatment policy	Hypothetical
Rationale for Strategies	To estimate effect irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. While alive strategy is used to reflect effect of treatment while alive.	To estimate effect as if there were no treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. While alive strategy is used to reflect effect of treatment while alive.

¹ Prohibited concomitant medications for this intercurrent event are botulinum toxin of any type, baclofen by intrathecal pump, and deep brain stimulation.

3.3.3. Secondary Efficacy Estimands

Secondary Efficacy Estimand 2 is defined as the difference (MTR-601– placebo) of mean change from baseline in TWSTRS severity, pain and disability score at the end of Week 4 in participants with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications. The difference of mean change from baseline in TWSTRS at the end of Week 4 is computed for all participants irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. In the event of a death, the difference of mean change from baseline in TWSTRS at the end of Week 4 will be calculated based on the available data while the participant was alive.

Secondary Efficacy Estimand 3 is defined as the difference (MTR-601– placebo) of mean change from baseline in TWSTRS overall, severity, pain and disability score at Week 2 in participants with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications. The difference of mean change from baseline in TWSTRS at Week 2 is computed for all participants irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication.

Table 3-2 Summary of Secondary Estimand and Strategies for Managing Intercurrent Events

Objective	Evaluate the effect of MTR-601 on other measures of efficacy	
Estimand Label	Estimand 2 (Secondary)	Estimand 3 (Secondary)
Estimand Description	Difference (MTR-601– placebo) of mean change from baseline in TWSTRS severity, pain and disability scores at the end of Week 4 in patients with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications.	Difference (MTR-601– placebo) of mean change from baseline in TWSTRS overall, severity, pain and disability scores at the end of Week 2 in patients with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications.
Target Population	Patients aged ≥ 18 to ≤ 70 years with a confirmed clinical diagnosis of cervical dystonia	Patients aged ≥ 18 to ≤ 70 years with a confirmed clinical diagnosis of cervical dystonia
Endpoint	Change from baseline in TWSTRS severity, pain and disability scores at the end of Week 4	Change from baseline in TWSTRS overall, severity, pain and disability scores at the end of Week 2

Objective	Evaluate the effect of MTR-601 on other measures of efficacy	
Estimand Label	Estimand 2 (Secondary)	Estimand 3 (Secondary)
Treatment	Test: MTR-601	Test: MTR-601
Condition(s)	Reference: placebo	Reference: placebo
Population-Level Summary	Difference (MTR-601–placebo) in the mean change from baseline at the end of Week 4	Difference (MTR-601–placebo) in the mean change from baseline at Week 2
Intercurrent Event Strategy		
1. Death	While alive	While alive
2. Discontinuation of Treatment	Treatment policy	Treatment policy
3. Dose Modification	Treatment policy	Treatment policy
4. Prohibited Concomitant Medication¹	Treatment policy	Treatment policy
Rationale for Strategies	To estimate effect irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. While alive strategy is used to reflect effect of treatment while alive.	To estimate effect irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. While alive strategy is used to reflect effect of treatment while alive.

¹ Prohibited concomitant medications for this intercurrent event are botulinum toxin of any type, baclofen by intrathecal pump, and deep brain stimulation.

3.4. Treatments

The two treatment groups are MTR-601 and placebo. IMP is MTR-601, a small-molecule inhibitor of myosin-2 “fast” isoform.

MTR-601 will be provided [REDACTED]

[REDACTED]. Each capsule will contain either no MTR-601 (placebo) or 40 mg of MTR-601 for oral dosing. During weeks 1 and 2, participants will take a total of 2 capsules once daily (a total dose of 80 mg of MTR-601 and matching placebo) and during weeks 3 and 4, the dosage level will go up to 4 capsules once daily (a total dose of 160 mg of MTR-601 and 0 mg of Placebo).

3.5. Dose Adjustment/Modifications

If there are persistent, clinically significant and/or substantially bothersome tolerability issues felt to be related to IMP at V5, the initial dose of 80 mg (2 capsules) may be maintained during week 3. At V6, if the tolerability issues remain, the initial dose of 80 mg (2 capsules) may be maintained during week 4, otherwise dose escalation to 160 mg (4 capsules) should occur.

Additionally, after the MTR-601 dose has been escalated to 160 mg after V5, participants who experience persistent, clinically significant and/or substantially bothersome tolerability issues felt to be related to IMP may undergo a dose reduction from 160 mg (4 capsules) to 80 mg (2 capsules) daily for improved tolerability. The following conditions must apply prior to the dose reduction, and the Sponsor medical team representative and the Medical Monitor must be consulted prior to dose reduction:

- The participant has completed at least 4 days of dosing at 160 mg.
- The participant has a TEAE of at least Grade 2 judged to be related to study treatment
- The participant has not met any stopping rule (see Section 7 of Protocol).
- The investigator feels that the participant would otherwise stop study treatment without dose reduction.

Following dose reduction, the participant will remain on 80 mg (2 capsules) qhs through the remainder of the study.

4. General Statistical Considerations

All data collected will be presented in data listings sorted by treatment and participant, and when appropriate by study visits within participants. Data from participants excluded from an analysis set will be presented in the data listings but will not be included in the calculation

of summary statistics for that analysis set. Summary tables will have a corresponding figure where applicable.

All continuous data will be summarized descriptively using means, standard deviations (SDs), medians, ranges (minimum, maximum, quartiles, etc.), and numbers of participants with data at each time point. All mean and median values will be formatted to one more decimal place than the actual value. SD values will be formatted to two more decimal places than the actual value. Minimum and maximum will be formatted to the same decimal place as the actual value.

When count data are presented, the percentage will be suppressed when the count is zero, in order to draw attention to the non-zero counts. Unless otherwise stated, the denominator for all percentages will be the number of participants in the given treatment group within the analysis set of interest and stratification level (if applicable) unless otherwise specified in a footnote. The number of missing values will be presented as a separate category but will only be displayed if one or more participants are missing data.

Categorical data will be tabulated and summarized using frequencies and proportions. All percentages will be rounded to one decimal place. The number and percentage will be presented in the form XX (XX.X), where the percentage is displayed in parentheses. For ordinal-scaled variables, a combination of frequency and percentage of observations within a category and means and standard deviations of the scores of the categories will be included. For categorical and ordinal variables, percentages will be calculated based on non-missing data. All statistical tests will be two-tailed and performed using a 5% significance level (with 95% 2-sided confidence intervals, CIs), unless otherwise indicated. All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be displayed as "< 0.0001", and if it is greater than 0.9999 it will be reported as ">0.9999".

For the purpose of analysis and presentation, the start day of treatment will be considered Study Day 1 and subsequent days numbered accordingly. Study Day is defined as (date of visit [event] – start date of treatment) + 1 for visit [event] on or after the start date of treatment. For visit [event] prior to the start date of treatment: (date of visit [event] – start date of treatment).

Unless specified otherwise, baseline will be defined as the last non-missing assessment (scheduled or unscheduled) prior to the administration of first dose of IMP. Both scheduled and unscheduled visits and assessments will be used in determining baseline. The change from baseline is calculated as the post-baseline value minus the baseline value.

All data processing, summarization, and analyses will be performed using SAS Environment/Version 9.4 or later of the SAS® statistical software package.

4.1. Sample Size

The sample size for this Phase 2a study was selected as deemed sufficient to generate an adequate safety, tolerability, and efficacy profile of MTR-601. With 40 participants in the MTR-601 group, there will be 87% chance of detecting at least one treatment-emergent adverse event (TEAE) for an adverse event with incidence rate of 5%, and > 98% chance of detecting at least one event with incidence rate of 10%.

With 40 participants per treatment group and assuming a dropout rate of 10%, this number of participants provides 82.2% power to detect a difference of -10.0 in the mean change from baseline in TWSTRS at the end of Week 4 between MTR-601 and placebo, assuming a common standard deviation of 14.5 and a two-sided 5% significance level. The power is 73.7% and 63.6% if the difference between MTR-601 and placebo is -9.0 and -8.0, respectively.

4.2. Randomization, Stratification, and Blinding

Up to 80 participants will be randomly assigned (ratio of 1:1) into 1 of 2 treatment arms: MTR-601 601 (80 mg during weeks 1-2, 160 mg during weeks 3-4) or matching placebo. The randomization will be stratified by clinical site to ensure balance across the treatment groups. To achieve this, an interactive response technology (IRT) system will be used to administer the randomization schedule. The randomization schedule will be created using SAS software Version 9.4 or higher (SAS Institute Inc, Cary, North Carolina) for the IRT system, which will link sequential participant randomization numbers to treatment codes.

To ensure blinding, capsules for each treatment arm as well as all specific doses will be presented in identical orange opaque capsules. Blinding for the initial phase will be maintained throughout the study until the final assessment for the final participants has been entered into the database and the database lock has been performed.

If participants are unblinded during the study, they will be summarized in a table and presented in a listing.

4.3. Analysis Sets

4.3.1. Screened Set

The Screened Set will comprise all participants who signed informed consent and attended screening Visit 1.

4.3.2. Screen Failure Set

The Screen Failure Set will comprise of all participants who consent to participate in the clinical study but are not subsequently randomized in the study.

4.3.3. Full Analysis Set (FAS)

The FAS will comprise all randomized participants. All analyses using the FAS will group participants according to randomized treatment. All efficacy analyses will be based on the FAS.

4.3.4. Safety Analysis Set (SAF)

The SAF will consist of all participants who received at least 1 dose of IMP(MTR-601 or placebo). All analyses using the SAF will group participants according to actual treatment received. All safety analyses will be based on the SAF.

4.3.5. Pharmacokinetics Analysis Set (PKS)

The PKS will consist of all participants in the SAF that have at least 1 post-treatment pharmacokinetics (PK) result.

5. Participant Disposition

5.1. Disposition

Participant disposition will be summarized for all screened participants. The number of participants screened, number of participants re-screened, enrolled but not randomized, number and percentage of participants randomized, number and percentage of participants who failed screening will be summarized by treatment group and overall.

Additionally, the number and percentage of participants who were randomized but not dosed (if any), who were dosed, who completed study treatment, who permanently discontinued study treatment, who completed study, and who permanently discontinued from the study

will be presented by treatment group and overall. The percentages for these frequencies will be based on the number of participants randomized. The reason for study treatment discontinuation and study discontinuation will also be summarized. The percentages for these frequencies will be based on the number of participants who discontinued study treatment or the study respectively. The frequency and percentage of participants who are ongoing at the time of a data freeze will also be summarized for intermediate analyses.

Also included in this summary will be the number and percentage of participants who were included in each analysis set, with percentages based on the number of participants randomized.

Participant disposition data will also be presented in a listing.

5.2. Protocol Deviations

According to ICH E3 [13], a protocol deviation is any change, divergence, or departure from the study design, or procedures defined in the protocol. Major (significant) protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. For example, major (significant) protocol deviations may include failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study or nonadherence to regulatory authority including ICH E6 (R2) guidelines [14]. Adherence to eligibility criteria as specified in the protocol is essential and deviations from the inclusion and exclusion criteria are not permitted because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The human research ethics committee/IRB should be notified of all protocol deviations, if appropriate, in a timely manner. Deviations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions put into place.

The major (significant) protocol deviations will be reviewed prior to database lock (DBL) and unblinding to determine which could potentially impact the scientific validity of the data collected. The frequency and percentage of participants with these "significant" protocol deviations will be tabulated by category and planned treatment group and overall. The percentages will be based on the number of participants in the FAS.

All protocol deviations will be also presented in a data listing, including the categorization of the deviation as major or not.

6. Demographics and Baseline Characteristics

6.1. Demographics

Summaries of demographics and stratification factors will be summarized for participants in the FAS and SAF by treatment group and overall. Demographics will also be summarized for participants in each site for both the FAS and SAF by treatment group and overall.

Demographic characteristics consist of:

- Age (continuous) in years
- Sex (Male, Female, Intersex, Unknown)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other pacific Islander, Other, Not Reported, Unknown, Multiple)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

Stratification factors consist of:

- Clinical Site

All demographic information will be presented as collected, in a data listing.

6.2. Baseline Characteristics

The following baseline characteristics will be summarized as continuous variables:

- Baseline body weight (kg)
- Baseline height (cm)
- Derived baseline body mass index (BMI, kg/m²)

The following baseline characteristics will be summarized as categorical variables:

- Females of Childbearing Potential (Yes, No)
- Serum Pregnancy Test Result (Positive, Negative, Not Done)

6.3. General Medical History

Medical history will be coded using the MedDRA (version to be delineated in the CSR). Medical history will be summarized by SOC and PT by treatment group and overall, for the participants in the SAF. Participant medical history will also be presented in a data listing.

6.4. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the study can be found in Sections 5.1 and 5.2 of the protocol [3], respectively. A listing of all inclusion criteria not met, and all exclusion criteria met will be presented for all participants by actual treatment group.

7. Treatments and Medications

7.1. Prior and Concomitant Medications and Therapies

All medications taken prior to signing the Informed Consent Form (ICF) are planned to be collected for the study including prior botulinum toxin and/or daxibotulinum ToxinA. Prior use of botulinum toxin and/or daxibotulinum ToxinA must be recorded in the concomitant therapy eCRFs. Prior medications are defined as medication used (i.e. the last day of use) prior to the first dose of the study treatment (Day 1) in the study. All prior medications will be summarized by treatment group and overall.

Concomitant medications are defined as all medications taken between the first date of the study treatment (Day 1) and end of follow-up/early termination (ET) of the study (Day 42). Concomitant medications will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Concomitant medications will be coded by the World Health Organization (WHO) Drug Dictionary (version to be delineated in the CSR). Concomitant medications will be summarized by ATC2 level, and preferred name by treatment group and overall, for the participants in the SAF.

Medications with a start or stop date on or after the first treatment dosing date will be considered concomitant medications. All medications which are ongoing will be considered concomitant. Concomitant medications will be summarized by treatment group and overall.

For the purpose of inclusion in concomitant medication tables, incomplete medication start and stop dates will be imputed as follows (where UK, UKN, and UNKN indicate unknown or missing day, month, and year, respectively):

Missing Start Dates

- First, remove any non-missing date component following any missing date component (e.g. set day to UK if month equals UKN or set month and day to UK and UKN, respectively, if year equals UNKN).
- UK-MMM-YYYY: Assume 01-MMM-YYYY, but if month and year are the same as the first dose of IMP month and year, then assume the date of first dose of IMP.
- UK-UKN-YYYY: Assume 01-JAN-YYYY, but if year is the same as the first dose of IMP year, then assume the date and month of first dose of IMP.
- UK-UKN-UNKN: Assume date of first dose of IMP.

Should the imputed start date fall after a complete stop date provided, use the stop date instead of the date that would otherwise be imputed.

Missing Stop Dates

- First, remove any non-missing date component following any missing date component (e.g. set day to UK if month equals UKN or set month and day to UK and UKN, respectively, if year equals UNKN).
- UK-MMM-YYYY: Assume the last day of the month.
- UK-UKN-YYYY: Assume 31-DEC-YYYY.
- UK-UKN-UNKN: Do not impute and assume ongoing.

Should the imputed stop date fall before a complete start date provided, use the start date instead of the date that would otherwise be imputed.

Concomitant medications will also be presented in a listing.

7.2. Prohibited Medications

Following randomization at Day 1/ Visit 3, the following medications are prohibited throughout the study:

Treatment for Cervical Dystonia:

- Botulinum toxin of any type
- Baclofen by intrathecal pump
- Deep brain stimulation

At Day 36 and thereafter, participants may resume treatment with botulinum toxin or daxibotulinum toxinA.

CYP3A4 inhibitors, inducers, and substrates

BCRP Substrates:

- rosuvastatin, sulfasalazine

Prohibited medications will be flagged based on the relevant PTs for the above medications in the prior and concomitant medication listing. The list of PTs will be identified prior to unblinding.

7.3. Study Treatments

7.3.1. Extent of Exposure

Study treatment exposure will be summarized for all participants in the SAF. Descriptive summaries of number and percentage of participants exposed to study treatment, missed doses, overdoses, partial (incomplete) doses as captured in EDC will be presented. Summaries will be provided by treatment group and overall.

Overall IMP compliance will be computed based on the number of capsules remaining in the bottle and the number of capsules missing for every participant as captured in EDC. It will be assumed that the number of capsules missing from the bottle were taken by the participant per protocol. Compliance will be calculated as:

$$Compliance (\%) = \frac{(n_d - n_r - n_m)}{N} \times 100$$

where,

N is the total number of capsules scheduled to be taken by a participant,

n_d is the total number of capsules dispensed,

n_r is the total number of capsules remaining in the bottle at the end of the study,

n_m is the total number of capsules reported as missing by the participant.

Participants are scheduled to take 2 capsules (80 mg) every day from Day 1 to Day 14. Following the in-clinic visit on Day 15, participants are scheduled to take 4 capsules (160 mg) every day until the end of treatment period on Day 29. Therefore, for all participants, N is expected to be 84 capsules from start of treatment to the last day of treatment provided no dose modification occurs through the duration of the study. If a participant undergoes dose reduction for experiencing persistent, clinically significant, and substantially bothersome tolerability issues that are felt to be related to study treatment, N will be calculated based on the modified dose. For participants who early terminated, the duration of the period before early termination will determine the total number of capsules scheduled to be taken (N). Compliance will then be calculated based on the actual number of capsules taken.

IMP compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for IMP compliance will be calculated out of the number of participants with non-missing observations. The percentages in these summaries will be based on the number of participants in the SAF.

A listing for IMP exposure and drug accountability will also be provided.

8. Efficacy Analysis

All efficacy analysis will be conducted on the FAS according to the planned treatment arms unless otherwise specified.

No multiplicity adjustment will be performed as only the primary efficacy hypothesis will be formally tested. Nominal p-values for other analyses will be reported.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the TWSTRS overall score change from baseline to the end of Week 4 (Treatment Period). TWSTRS score for pain, severity and disability will be collected in-clinic during screening (Visit 2), at baseline (Visit 3), Day 15 (Visit 5), Day 29 (Visit 7) and at the end of follow-up on Day 42 (Visit 8). A modified TWSTRS score for pain and disability in sub-scales will be conducted at home on Day 8 (Visit 4) and Day 22 (Visit 6). The maximum subtotal score for severity, disability and pain is 35, 30 and 20 respectively. The TWSTRS overall score is calculated as a sum of the three subtotal scores.

8.2. Primary Efficacy Hypotheses

The null and alternative hypotheses for the primary efficacy objective are:

$$H_0: \mu_{MTR} - \mu_{PBO} \geq 0$$

$$H_a: \mu_{MTR} - \mu_{PBO} < 0$$

where μ_{MTR} is the true mean change from baseline in TWSTRS overall score at the end of Week 4/ Day 29 (Visit 7) in the MTR-601 group, and μ_{PBO} is the true mean change from baseline in TWSTRS overall score at the end of Week 4/ Day 29 (Visit 7) in the placebo group. The hypotheses will be evaluated using a two-sided test at an alpha level of 0.05.

8.3. Primary Analysis of Primary Efficacy Endpoint (Estimand 1a)

A mixed model for repeated measures (MMRM) will be fit to the change from baseline to the end of Week 4 in TWSTRS overall scores. The model will include the following fixed-effect terms:

- Treatment arm
- Baseline TWSTRS overall score

- Visit
- Interaction term of treatment and visit

The covariances between repeated measures on participants will be incorporated in the model with an unstructured covariance matrix. Should the model fail to converge, then the following structures will be used in a sequential manner, and the first that successfully converges will be selected: heterogeneous Toeplitz, Toeplitz, and compound symmetry. Per the primary estimand 1a, data will be collected regardless of treatment discontinuation. In the case of participant death, the last value prior to death will be carried forward and used to calculate changes from baseline following death to facilitate modeling.

No imputation of missing data will be performed for the main analysis, which assumes that any missing data are missing at random (MAR), and early termination due to Sponsor decision will be handled using the MMRM approach under the MAR assumption.

With this model, the change in TWSTRS overall score at the end of Week 4 from baseline will be compared between MTR-601 group and the placebo group among all participants in the FAS. The primary analysis will summarize the pairwise comparison (i.e. mean difference between MTR-601 group and placebo) to include: the least square mean estimates and standard error (SE) for each treatment group at Week 4, the 95% CI of the least square means, the difference in the least square means and its SE, the 95% CI of the difference, and the 2 sided p-value derived from the model. The time course of the intervention effect for participants in each treatment group will be plotted using a line plot. The mean TWSTRS overall score (on the y-axis) will be plotted against the analysis visit (on the x-axis), differentiated using unique colors for each treatment group.

8.4. Supplementary Analysis of Primary Efficacy Endpoint (Estimand 1b)

An MMRM model will be fit to the change from baseline to the end of Week 4 in TWSTRS overall scores, with the same fixed-effect terms as the primary estimand 1a. Strategies in the event of non-convergence will also mimic those of the main analysis. In order to support the hypothetical strategy for intercurrent events of treatment discontinuation, dose modification, or use of prohibited concomitant medications, data collected following intercurrent events will be censored. In the case of participant death, the last value prior to death will be carried forward and used to calculate changes from baseline following death to facilitate modeling. No imputation of missing or censored data will be performed for the supplementary analysis, which assumes that any missing or censored data are missing at random.

A summary table and figure similar to the Primary Estimand 1a, will be presented.

8.5. Sensitivity Analysis of Primary Efficacy Endpoint (Estimand 1a)

A sensitivity analysis will be conducted utilizing Analysis of Covariance (ANCOVA) and a multiple imputation (MI) method targeting intercurrent events with a treatment policy strategy.

The imputation of missing TWSTRS scores will be carried out in a 2-step fashion:

1. **MI Step 1 (MCMC):** In the case of no intermittent missing data, this step will be skipped and Step 2 will instead generate the 100 multiply imputed datasets directly.

Multiple imputation models under the MAR assumption will be performed to impute intermittent missing values separately for each randomized group based on a multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than 0. In the event that the model fails to impute variables for the specified minimum value, log-transformed variables will be used in the model without stating any minimum. The variables will be back transformed after imputation. The seed number will be set to 590267. The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior with 100 imputations.

2. **MI Step 2 (MONOTONE):** MI based on retrieved dropouts approach under missing not at random (MNAR) assumption with seed 8243207 will then be applied to generate a single imputation for each of the 100 multiply imputed datasets under MI Step 1. The remaining, monotone missing data for all participants will be imputed using information from retrieved dropouts. Retrieved dropouts are defined as participants who remain in the study despite occurrence of intercurrent events of treatment discontinuation, dose modification, or use of prohibited medication [15]. The imputation will be performed adjusting for baseline and prior TWSTRS scores. The monotone missing data after the occurrence of an intercurrent event with treatment policy will be imputed using sequential regression multiple imputation model estimated based on data from retrieved dropouts only.

As elsewhere, the minimum values for imputed variables will be set to 0 but if the model fails to perform imputation based on the minimum criteria, log-transformed

variables will be used in the model without stating any minimum. The variables will be back transformed after imputation.

In the event of non-convergence due to small sample size, multiple imputation using copy reference approach with placebo as reference will be used for MI Step 2. Imputation of values in the experimental arm (MTR-601) will be done as if the participant had been a member of the reference arm. Imputed values in the experimental arm will be sampled using the imputation model of the reference arm, i.e., conditional on participant values observed at time points prior to discontinuation relative to the mean of the model for the reference arm. The seed number will be set to 8243207. The monotone missing data after the occurrence of an intercurrent event with treatment policy will be imputed using sequential regression multiple imputation model estimated based on data from placebo participants only.

If the model does not converge even after model simplification, the sensitivity analysis will not be conducted.

Upon successfully performing multiple imputation, change from baseline in TWSTRS overall score will be calculated using imputed values. The ANCOVA model will include treatment as a factor and adjusted for baseline TWSTRS overall score and site. The analysis will be conducted on all 100 multiply imputed datasets. The results for each of these 100 datasets will be combined using Rubin's rule to obtain an overall confidence interval and p-value for difference in means while accounting for missing data.

The result from the analysis namely the Least Square (LS) Means, SEs, corresponding 95% CI, difference in LS Means, corresponding 95% CI and p-value will be presented in a summary table.

8.6. Secondary Analysis of Secondary Efficacy Endpoints (Estimand 2 and 3)

The secondary endpoints of change in TWSTRS score for severity, pain and disability from baseline to the end of Week 4 will be analyzed in the same way as the primary endpoint. Each TWSTRS score scale will be modeled separately. An MMRM will be fit to the change from baseline to the end of Week 4 in TWSTRS scores for severity, pain and disability. The model will include the same fixed-effect terms and unstructured covariance matrix as the primary endpoint. Should the model fail to converge, then the following structures will be

used in a sequential manner, and the first that successfully converges will be selected: heterogeneous Toeplitz, Toeplitz, and compound symmetry. Individual summary tables and figures for each score (namely, score for severity, pain and disability) will be presented.

The secondary endpoints of change in TWSTRS score for severity, pain and disability and TWSTRS overall score from baseline at Week 2 will also be analyzed in the same method described above. Summary tables and figures from the analysis will be presented.

8.7. Exploratory Analysis

The following exploratory endpoints will be summarized descriptively:

- CDQ-24, TSQM, CGI-S and CGI-C results at the end of Weeks 2 and 4
- PGI-S and PGI-C results at the end of Week 1, 2, 3, and 4.
- TWSTRS pain and disability scores at the end of Week 1 and 3 based on the modified TWSTRS scale (as per Appendix: Schedule of Assessments).

9. Safety Analysis

All safety summaries and analyses will be performed using the SAF.

All safety data collected will be included in the applicable summaries regardless of whether a participant has received incorrect treatment provided the participant is included in the SAF. Descriptive summaries of all applicable safety data will be provided. All collected safety data will also be presented in a listing.

No statistical hypotheses will be tested for the primary safety and tolerability objective.

9.1. Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant administered with an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal clinical laboratory finding, for example), symptoms, or disease temporally associated with the use of an IMP, whether or not related to the IMP. An AE may be:

- A new illness,
- Worsening of a concomitant illness,

- An effect of the IMP including comparator; it could be an abnormal clinical laboratory value as well as a significant shift from baseline within normal range which an Investigator considers to be clinically important.

Surgical procedures themselves are not AEs. AEs will be recorded from the ICF signature through 90 days after last dose of IMP.

A treatment emergent adverse event (TEAE) is an adverse event (AE) with a start date on or after the date of treatment. The percentage of participants with TEAEs throughout the study will be summarized for MTR-601 and placebo as well as overall. The incidence and frequency of TEAEs will be tabulated, and TEAEs will be listed using the SAF.

TEAEs will be summarized by system organ class (SOC) and preferred term (PT) using MedDRA coding (version to be delineated in the CSR). TEAEs throughout the study will be summarized by severity, seriousness, and relationship to IMP for each treatment group and overall.

Incidence tables will include counts and percentages. Incidence tables will count each participant only once for each SOC and PT and the denominator of percentages will be set to the number of participants in the SAF in each column. Total event counts will also be included.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed according to the below rules (where UK, UKN, and UNKN indicate unknown or missing day, month, and year, respectively):

Missing Onset Dates

- First, remove any non-missing date component following any missing date component (e.g. set day to UK if month equals UKN or set month and day to UK and UKN, respectively, if year equals UNKN).
- UK-MMM-YYYY: Assume 01-MMM-YYYY, but if month and year are the same as the first dose of IMP month and year, then assume the date of first dose of IMP.
- UK-UKN-YYYY: Assume 01-JAN-YYYY, but if year is the same as first dose of IMP year, then assume the date and month of first dose of IMP.
- UK-UKN-UNKN: Assume date of first dose of IMP.

Should the imputed start date fall after a complete stop date provided, use the stop date instead of the date that would otherwise be imputed.

Missing End Dates

- First, remove any non-missing date component following any missing date component (e.g. set day to UK if month equals UKN or set month and day to UK and UKN, respectively, if year equals UNKN).
- UK-MMM-YYYY: Assume the last day of the month.
- UK-UKN-YYYY: Assume 31-DEC-YYYY.
- UK-UKN-UNKN: Do not impute and assume ongoing.

Should the imputed stop date fall before a complete start date provided, use the start date instead of the date that would otherwise be imputed.

All TEAEs will also be presented in a data listing.

9.1.1. Overall Summary of Adverse Events

A summary of TEAEs will be tabulated by treatment group and overall, by providing the number and percent of participants who experience the following:

- Participants with at least one TEAE
- Participants with at least one related TEAE
- Participants with at least one TEAE by severity
- Participants with at least one serious TEAE
- Participants with at least one serious related TEAE
- Participants with at least one serious TEAE by severity
- Participants with at least one AESI
- Participants with TEAE leading to treatment discontinuation
- Participants with TEAE leading to study discontinuation
- Participants with TEAE with an outcome of death

9.1.2. Incidence of Adverse Events

The incidence and frequency of TEAEs will be summarized by SOC and PT. The number and percentage of participants and number of events will be presented for each treatment group and overall. Adverse events will also be listed.

9.1.3. Relationship of Adverse Events to IMP

The investigator's assessment of an AE's relationship will be characterized using classification of "Reasonably Possible" or "Not Reasonably Possible".

Reasonable
Possibility:

A temporal relationship exists between the AE onset and administration of the IMP that cannot be readily explained by the participant's clinical state or concomitant therapies.

Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the IMP.

In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.

No Reasonable
Possibility:

Evidence exists that the AE has an etiology other than the IMP.

For Serious AEs (SAEs), an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

The incidence of TEAEs will be tabulated by SOC and PT and relationship to IMP for each treatment group and overall. Incidence will be based on the worst relationship within each level of summarization.

The incidence of related (Reasonable Possibility, No Reasonable Possibility) TEAEs will also be tabulated by SOC and PT. TEAEs that are missing relationship will be presented in tables as having "Reasonable Possibility" but will be presented in the data listing with a missing relationship.

9.1.4. Severity of Adverse Event

All AEs will be graded per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities. The severity of the AE will be rated as CTCAE Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially Life-threatening), or Grade 5 (fatal/death).

<u>Grade 1 (mild):</u>	An AE with asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
<u>Grade 2 (moderate):</u>	An AE with minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
<u>Grade 3 (severe):</u>	An AE which is severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
<u>Grade 4 (potentially life-threatening)</u>	An AE with life-threatening consequences; urgent intervention indicated.
<u>Grade 5 (fatal/death)</u>	Death related to AE.

The incidence of TEAEs will be tabulated by SOC and PT and severity for each treatment group and overall. Incidence will be based on the worst severity within each level of summarization. In the TEAE severity table, if a participant reported multiple occurrences of the same TEAE, only the most severe will be presented. TEAEs that are missing severity will be presented in tables as CTCAE Grade 3 (Severe) but will be presented in the data listing with a missing severity. Percentages will be calculated based on the number of participants in the SAF in each treatment group.

Any changes in the severity/intensity of an AE will be documented as a new AE with updated severity to allow for the assessment of the duration of the event at each grade of severity/intensity.

9.1.5. Serious Adverse Events

A SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,

- Is an important medical event that may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of an Investigator).

SAEs will be recorded from the ICF signature through 90 days after last dose of IMP. The incidence and frequency of serious TEAEs will be summarized by SOC and PT for each treatment group and overall. Serious TEAEs will also be presented by relationship and severity. SAEs will also be presented in a listing.

9.1.6. Adverse Events Leading to Treatment Discontinuation

The incidence of TEAEs leading to treatment discontinuation will be summarized for each treatment group and overall by SOC and PT. A corresponding listing will also be presented.

9.1.7. Adverse Events Leading to Study Discontinuation

The incidence of TEAEs leading to study discontinuation will be summarized for each treatment group and overall by SOC and PT. A corresponding listing will also be presented.

9.1.8. Adverse Events with an Outcome of Death

A summary of TEAEs where the answer to “Outcome” is “Death Related to Adverse Event” will be presented in a table. At each level of summarization, a participant is counted once if the participant reported one or more events. Percentages will be calculated based on the number of participants in the SAF in each treatment group. A similar summary will be presented for all fatal TEAEs that are deemed as related to the IMP.

The incidence of TEAEs leading to death will be summarized for each treatment group and overall by SOC and PT. All participants who have a TEAE with an outcome of “Death Related to Adverse Event” will be presented in a listing.

9.1.9. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs of scientific or medical concern. These may include events that are either specific to the IMP or events that, in general, may be of clinical significance with any medicinal product under development. As such, an AESI may or may not be related to the IMP.

AESIs will be presented by SOC and PT. At each level of summarization, a participant is counted once if the participant reported one or more events. Percentages will be calculated based on the number of participants in the SAF in each treatment group and overall.

The following events are identified as AESIs:

- Elevation in creatinine or BUN of $\geq$ grade 2 severity
- Drowsiness (or similar terms) of $\geq$ grade 2 severity
- Muscle weakness (or similar terms) of $\geq$ grade 2 severity
- Visual disturbance (or similar terms) of any severity
 - A dedicated ophthalmologic examination should take place as soon as is practicable to document and characterize any abnormality in eye movement or function.

9.2. Clinical Laboratory Evaluations

Laboratory tests for hematology, serum chemistry, urinalysis, coagulation, and serology, and pregnancy will be collected and summarized. The incidence of laboratory abnormalities by laboratory test type will be summarized by treatment group and overall. All laboratory abnormalities will also be presented in a listing.

Summary statistics for change from baseline in laboratory test results will be tabulated by scheduled visit for each treatment group and overall. All laboratory test results will be provided in a listing by laboratory test type.

9.2.1. Hematology

The following hematology laboratory tests will be performed at screening (Week -14 to -1), Visit 5 (Week 2), Visit 7 (Week 4) and Visit 8 (Week 6):

- White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil)
- Red cell count
- Hemoglobin
- Hematocrit
- Mean Corpuscular Volume
- Platelet Count

9.2.2. General Biochemistry

The following hematology laboratory tests will be performed at screening (Week -14 to -1), Visit 5 (Week 2), Visit 7 (Week 4) and Visit 8 (Week 6):

- Alanine aminotransferase
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase
- Bilirubin total and conjugated bilirubin if total bilirubin is elevated
- Blood urea nitrogen
- Calcium
- Chloride
- Creatinine phosphokinase (CPK)
- Bicarbonate (CO₂)
- Creatinine (including eGFR calculated using the CKD EPI calculation)
- Cholesterol total
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorous
- Potassium
- Protein total
- Sodium
- Triglycerides
- Uric acid
- Gamma-glutamyl transpeptidase (GGT)

9.2.3. Coagulation

The following coagulation laboratory tests will be performed at screening (Week -14 to -1), Visit 5 (Week 2), Visit 7 (Week 4) and Visit 8 (Week 6):

- Prothrombin time
- International normalized ratio (INR)
- Partial Thromboplastin Time (aPTT) levels

9.2.4. Other Laboratory Tests

A serum pregnancy test will be performed on all women of childbearing potential at screening, and must yield a negative result for a participant to be randomized to the study. Participants will undergo additional urine pregnancy tests at screening (Week -14 to -1) Visit 5 (Week 2), Visit 7 (Week 4) and Visit 8 (Week 6). All urine pregnancy test results will be presented in a summary table and listing.

Blood samples for measuring Follicle-Stimulating Hormone (FSH) in order to confirm menopause, for all women who are not of childbearing potential will be collected at screening. All results will be presented in a listing.

Blood serum samples will also be evaluated for testing Human immunodeficiency virus (HIV) Ag/Ab Combo, Hepatitis B surface antigen, and Hepatitis C virus (HCV).

Urine alcohol and drug screening to determine the presence of the following will be collected at screening:

- Alcohol (ethylglucuronide)
- Amphetamines
- Methamphetamines
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine
- Cotinine
- Methadone
- Opiates
- Oxycodone
- Fentanyl
- Buprenorphine
- Phencyclidine

All test results from urine alcohol and drug screening will be presented in a listing.

Additionally, urinalysis will also be conducted for testing color, appearance, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, and urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the

reference range for leukocyte, blood, nitrite, or protein. All results from urinalysis will be presented in a listing.

9.3. Vital Sign Measurements

Vital sign measurements will be obtained at the visits designated in the [14.1 Appendix: Schedule of Assessments](#). Vital signs will be measured in a seated position after 5 minutes rest. These measurements will include the following:

- Body temperature (C)
- Respiratory rate (breaths/min)
- Pulse rate (beats/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg).

Each participant's baseline body weight (kg), height (cm) and BMI will be collected during Screening (weeks -14 to -1). Subsequently, body weight (kg) measurements will be obtained at the visits designated in the [Appendix: Schedule of Assessments](#). BMI will be calculated as follows: $BMI = \text{weight (kg)} / [\text{height (m)}]^2$ at each subsequent visit using baseline height.

For each abnormal vital sign value, the Investigator will determine whether to report an AE. Additional tests and evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the Investigator.

Change from baseline in vital signs will be summarized by scheduled visit for each treatment group and overall. A listing of vital signs will also be provided.

9.4. Physical Examination

Physical examinations (full, limited) will be performed as specified in the [Appendix: Schedule of Assessments](#). The physical examination will include examinations of the following body systems: Oral, Neck, Gastrointestinal (Abdomen), Ear, Nose, Mouth, and Throat, Skin, Musculoskeletal, Respiratory System, Extremities, Lymphatic, Cardiovascular, Head and Face, Breast, Genitourinary, and Eye.

A table will summarize physical examination results by treatment group and overall for the SAF. The summary will include the number and percentage of participants with each PE

outcome: Normal, Abnormal (Not Clinically Significant), Abnormal (Clinically Significant), per body system.

All physical examination abnormalities will also be presented in a listing.

9.5. Electrocardiogram

Electrocardiogram (ECG) interpretation will be categorized as normal, abnormal not clinically significant, and abnormal clinically significant. A 12-lead ECG will be performed at Visit 1 (Screening), Visit 7 (Week 4), and Visit 8 (Week 6). ECG parameters include heart rate, PR interval, QRS interval, QT interval, QTcB interval (Bazett's correction), and QTcF interval (Fridericia's correction). Observed ECG results will be tabulated by visit for each treatment group and overall. A listing of ECG results will also be provided.

10. Pharmacokinetics

The concentrations of MTR-601 will be assessed based on blood collected from participants during the study at the visits designated in the [Appendix: Schedule of Assessments](#). A summary table will be presented with concentration descriptive statistics for: n (count), mean, SD, CV%, median, minimum, and maximum for all participants in the PKS. Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics.

Plasma concentrations for each participant will also be listed.

11. Interim Analysis

No interim analyses are planned.

12. Changes in the Planned Analysis

All prior medications will be collected for all participants who sign the ICF for the study and will be summarized by treatment group and overall. However, the protocol does not specify the collection and summarization of prior medications except botulinum toxin and/or daxibotulinum ToxinA.

All participants who receive at least one dose of study treatment will have their total number of capsules taken (N) recorded and summarized by treatment group and overall. However, the protocol does not specify a fixed N for participants who terminate early; therefore, for

these participants, N will be based on the actual number of capsules taken during the study treatment. Pooled site has been excluded from the estimand models. As each site includes a very small number of participants, its removal helps to improve the model stability and convergence.

PK analyses by age category will not be performed due to the small number of participants.

Early termination due to Sponsor decision will be handled using the MMRM approach under the missing at random (MAR) assumption.

13. References

1. ICH. Guidance for Industry (E9 Statistical Principles for Clinical Trials)
2. ICH. Guidance for Industry (E9(R1)) Addendum on estimands and sensitivity analysis in clinical trials to the guidance on statistical principles for clinical trials)
3. Protocol MTR 601-201 “A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of MTR-601, a Novel Oral Treatment in Patients with Cervical Dystonia”
4. Albanese, A., et al., Isolated Cervical Dystonia: Diagnosis and Classification. *Mov Disord*, 2023. 38(8): p. 1367-1378.
5. Anandan, C. and J. Jankovic, Botulinum Toxin in Movement Disorders: An Update. *Toxins (Basel)*, 2021. 13(1).
6. Aradi, S. and R.A. Hauser, Current use of neurotoxins for alleviating symptoms of cervical dystonia. *Expert Rev Neurother*, 2024. 24(8): p. 787-797.
7. Comella, C.L., et al., Efficacy and Safety of DaxibotulinumtoxinA for Injection in Cervical Dystonia: ASPEN-1 Phase 3 Randomized Controlled Trial. *Neurology*, 2024. 102(4): p. e208091.
8. Balint, B., et al., Dystonia. *Nat Rev Dis Primers*, 2018. 4(1): p. 25.
9. Jankovic, J., J. Tsui, and M.F. Brin, Treatment of cervical dystonia with Botox (onabotulinumtoxinA): Development, insights, and impact. *Medicine (Baltimore)*, 2023. 102(S1): p. e32403.
10. Marsili, L., et al., Long-term efficacy and safety of botulinum toxin treatment for cervical dystonia: a critical reappraisal. *Expert Opin Drug Saf*, 2021. 20(6): p. 695-705.
11. Bellows, S. and J. Jankovic, Immunogenicity Associated with Botulinum Toxin Treatment. *Toxins (Basel)*, 2019. 11(9).

12. Dashtipour, K., et al., Treatment response to onabotulinumtoxinA in cervical dystonia patients with anterocollis and retrocollis. *Toxicon*, 2024. 248: p. 108035.
13. ICH. Topic E3. Note for guidance on structure and content of clinical study reports.
14. ICH. Guidance for Industry (Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6 (R2)).
15. Wang, S., Hu, H. Impute the missing data using retrieved dropouts. *BMC Med Res Methodol* 22, 82 (2022). <https://doi.org/10.1186/s12874-022-01509-9>

14. Appendices

14.1. Appendix: Schedule of Assessments

	Screening 90 days		Treatment 4 weeks				Follow- Up/ET ¹⁴ 2 weeks	
Week	-12 to -1	-2 to -1	1	2	3	4	6	
Day	-90 to -2	-16 to -1	1	8 ± 2	15 ± 2	22 ± 2	29 ± 2	42 ± 2
Visit Number	V1 ¹	V2	V3	V4	V5	V6	V7	V8
In-Clinic Visit		X	X		X		X	X
Home-Based Telehealth Visit ²	X			X		X		
Informed Consent Obtained	X							
Inclusion/Exclusion Criteria	X	X	X ³					
Demographics		X						
Medical History	X ⁴	X						
IRT-Randomization			X					
IMP Dispensation			X					
IMP Administration ⁵			X					
IMP Accountability ⁶				X	X	X	X	
Adverse Events	X							
PK Sampling, Plasma					X		X	X
TWSTRS ⁷		X	X	X	X	X	X	X
CDQ-24 (PRO)			X	X	X	X	X	X
TSQM (PRO)				X	X	X	X	X
CGI-S (ClinRO) & PGI-S (PRO)			X	X	X	X	X	X
CGI-C (ClinRO) & PGI-C (PRO)				X	X	X	X	X
(Optional) Blood Sample for Genetics			X					
Physical Exam ⁸		X			X		X	X
Vital Signs		X	X		X		X	X
Body Weight, Height and BMI ¹⁰		X						X
12 Lead ECG ¹¹		X					X	X
Concomitant Medications		X						
UDS		X ¹²						
Serology		X						
FSH		X						
General Biochemistry		X			X		X	X
Coagulation		X			X		X	X
Hematology		X			X		X	X
Urinalysis		X			X		X	X
Pregnancy Test ¹³		X			X		X	X

¹V1 may be completed up to 90 days before the baseline (V3). V1 and V2 may be completed on the same day in clinic between Day-16 to Day-2.

²At scheduled telehealth visits (V1, V4, V6) participants can instead choose to come in person to the clinic. Participants who undergo a telehealth visit at V1 will have informed consent conducted remotely.

³Confirmation that the participant has completed the protocol-defined washout period botulinum toxin and/or daxibotulinum toxin injections. Re-confirmation of other inclusion and exclusion criteria is not necessary.

⁴A limited medical history only is needed at Screening V1 to confirm the participant is receiving or has received botulinum toxin for Cervical Dystonia and to confirm when the next scheduled treatment is due to plan for timing of V2.

⁵IMP is an orange opaque capsule (MTR-601 40 mg or matching placebo) for oral administration, dosed qhs. Weeks 1-2, dose will be 2 capsules (80 mg or placebo); Weeks 3-4, dose will be 4 capsules (160 mg or placebo).

⁶IMP accountability at V4 and V6 will include re-training with dosing instructions and verbal confirmation that each daily dose has been taken. At V5 IMP accountability will include re-training with dosing instructions and manual pill counts, and at V7 a final manual pill count will take place.

⁷TWSTRS including only the Disability and Pain sub-scales will be conducted at home at V4 and V6. Participants can instead choose to come in person to the clinic. (See Protocol Section 8.2.1).

⁸Full physical exam at V2 only. A limited physical exam will be performed at all other visits (see Protocol Section 8.3.1).

⁹ Vital signs will be measured in a seated position after 5 minutes rest.

¹⁰ Height and BMI, done only at Screening Visit 2.

¹¹The ECG will be recorded while the participant is resting in a supine position for at least 5 minutes and will electronically measure the PR, QRS, and QT intervals, QTcB, QTcF, and heart rate. The ECG can be repeated once at V2 at the discretion of the investigator and used for eligibility determination.

¹²Laboratory assessments for study eligibility include UDS, serology, general biochemistry, coagulation, hematology, urinalysis, serum pregnancy and FSH for confirmation of menopause where applicable. . A complete list of laboratory assessments can be found in Protocol Section 10.2.

¹³Screening (V2) will be a serum β -hCG test; All other visits (V5, V7, V8) will be a urine β -hCG test.

¹⁴At Day 36 and thereafter, participants may resume treatment with botulinum toxin or daxibotulinum toxinA

14.2. Appendix: Analysis Visit Windows for Efficacy Analyses

Visit windows for TWSTRS, CDQ-24, CGI-S, PGI-S, CGI-C, and PGI-C are presented below.

Visit	Week	Target Day	Analysis Visit Window
Visit 3	Baseline	≤ Study Day 1	≤ Study Day 1 (prior to treatment start)
Visit 4	Week 1	Study Day 8	Study Day 2 to Study Day 11
Visit 5	Week 2	Study Day 15	Study Day 12 to Study Day 18
Visit 6	Week 3	Study Day 22	Study Day 19 to Study Day 25
Visit 7	Week 4	Study Day 29	Study Day 26 to Study Day 35
Visit 8	Follow-up	Study Day 42	Study Day 36 to Study Day 44

If multiple assessments occur within the same window, the assessment closest to the target study day will be used. In the case of multiple assessments with the same difference from target day, the latest assessment will be used. All visits including scheduled, unscheduled and early termination visits will be subject to the analysis visit windows.

14.3. Appendix: TWSTRS Scale

Severity Subscale	
A. Maximum Excursion: Rate the maximum amplitude of excursion, asking the patient not to oppose the abnormal movements; examiner may use distracting or aggravating maneuvers. If degree of deviation is between 2 scores, choose the higher of the 2.	
1. Rotation (turn right or left) 0= None 1= Slight (< ¼ range) (1-22 degrees) 2= Mild (¼ – ½ range) (23-45 degrees) 3= Moderate (½ – ¾ range) (46-67 degrees) 4= Severe (> ¾ range) (68-90 degrees)	
2. Laterocollis (tilt right or left; exclude shoulder elevation) 0= None 1= Mild (1-15 degrees)	

2= Moderate (16-35 degrees) 3= Severe (> 35 degrees)	
3a. Anterocollis 0= None 1= Mild downward deviation of the chin 2= Moderate downward deviation (approximately ½ possible range) 3= Severe (chin approximates chest)	
3b. Retrocollis 0= None 1= Mild backward deviation of the vertex with upward deviation of the chin 2= Moderate backward deviation (approximately ½ possible range) 3= Severe (approximately full range)	
4. Lateral shift (right or left) 0= Absent 1= Present	
5. Sagittal shift (forward or backward) 0= Absent 1= Present	
B. Duration Factor: Provide an overall score estimated throughout the course of the standardized examination after estimating maximal excursion (i.e., exclusive of asking patient to allow head to deviate maximally). <i>Weighted x 2.</i> 0= None 1= Occasional deviation (< 25% of the time); most often submaximal 2= Occasional deviation (<25% of the time); often submaximal or intermittent (25-50% of the time); most often submaximal 3= Intermittent (25-50% of the time); often submaximal or frequent (50-75% of the time); most often submaximal 4= Frequent (50-75% of the time); often submaximal or constant (>75% of the time); most often submaximal 5= Constant (>75% of the time); often submaximal	
C. Effect of Sensory Tricks	

0= Complete relief by use of one or more tricks 1= Partial, or only limited, relief by use of tricks 2= Little or no benefit from use of tricks	
D. Shoulder Elevation/Anterior Displacement 0= Absent 1= Mild: Intermittent or constant (< 1/3 possible range) 2= Moderate (1/3- 2/3 possible range) and constant (>75% of the time) or severe and intermittent (>2/3 possible range) 3= Severe and constant	
E. Range of Motion (without aid of sensory tricks): If limitation occurs in more than one plane of motion, use individual score that is the highest. 0= Able to move to extreme opposite position 1= Able to move head well past midline, but not to extreme opposite position 2= Able to barely move head past midline 3= Able to move head toward but not past midline 4= Barely able to move head beyond abnormal posture	
F. Time: Time (up to 60 seconds) for which patient is able to maintain head within 10 degrees of neutral position without the use of sensory tricks (mean of 2 attempts) 0= >60 seconds 1= 46-60 seconds 2= 31-45 seconds 3= 16-30 seconds 4= <15 seconds	
Pain Subscale	
A. Severity: Rate the severity of neck pain during the last week, on a scale of 0-10, where a score of 1 represents a minimal ache and 10 represents the most excruciating pain imaginable. Pain Severity Score = [(best+worst+2*usual)]/4 Usual (0-10) Best (0-10)	_____

Worst (0-10)	
B. Duration (rate the duration of neck pain) 0= None 1= Present <10% of the time 2= Present 10% to <25% of the time 3= Present 25% to <50% of the time 4= Present 50% to <75% of the time 5= Present >75% of the time	
C. Disability (the degree to which pain contributes to disability) 0= No limitation or interference from pain 1= Pain is quite bothersome, but not a source of disability 2= Pain definitely interferes with some tasks, but is not a major contributor of disability 3= Pain accounts for some (less than half) but not all disability 4= Pain is a major source of difficulty with activities, separate from this, head pulling is also a source of some (less than half) disability 5= Pain is a major source of disability; without it, most impaired activities could be performed quite satisfactorily despite the head pulling	
Disability Subscale	
A. Work (occupation or housework/home management) 0= No difficulty 1= Normal work expectations with satisfactory performance at usual level of occupation, but some interference by torticollis 2= Most activities unlimited; selected activities very difficult and hampered, but still possible with satisfactory performance 3= Working at lower than usual level of occupation; most activities hampered: all possible but less than satisfactory performance in some activities 4= Unable to engage in voluntary or gainful employment; still able to perform some domestic responsibilities satisfactorily 5= Marginal or no ability to perform domestic responsibilities	

B. Activities of Daily Living (e.g., eating, dressing, hygiene [including washing, shaving, applying make-up, etc.]) 0= No difficulty with any activity 1= Activities unlimited, but some interference by torticollis 2= Most activities unlimited; selected activities very difficult and hampered, but still possible using simple tricks 3= Most activities hampered or laborious but still possible; may use extreme tricks 4= All activities impaired; some impossible or require assistance 5= Dependent on others in most self-care tasks	
C. Driving 0= No difficulty (or has never driven a car) 1= Unlimited ability to drive, but bothered by torticollis 2= Unlimited ability to drive, but requires tricks (including touching or holding face, holding head against head rest) to control torticollis 3= Can drive only short distances 4= Usually cannot drive because of torticollis 5= Unable to drive and cannot ride in car for long stretches as a passenger because of torticollis	
D. Reading 0= No difficulty 1= Unlimited ability to read in normal seated position, but bothered by torticollis 2= Unlimited ability to read in normal seated position, but requires use of tricks to control torticollis 3= Unlimited ability to read, but requires extensive measures to control torticollis or only able to read in non-seated position (e.g., lying down) 4= Limited ability to read because of torticollis despite tricks 5= Unable to read more than a few sentences because of torticollis	
E. Television 0= No difficulty 1= Unlimited ability to watch television in normal seated position, but bothered by torticollis 2= Unlimited ability to watch television in normal seated position, but requires use of tricks to control torticollis	

3= Unlimited ability to watch television, but requires extensive measures to control torticollis or only able to watch in non-seated position (e.g., lying down) 4= Limited ability to watch television because of torticollis 5= Unable to watch television for more than a few minutes because of torticollis	
F. Activities Outside the Home (e.g., shopping, walking, movies, dining, and other recreational activities) 0= No difficulty 1= Unlimited activities, but bothered by torticollis 2= Unlimited activities, but requires use of simple tricks to accomplish them 3= Only accomplishes activities when accompanied by others because of torticollis 4= Limited activities outside the home; certain activities impossible or given up due to torticollis 5= Rarely, if ever, engages in activities outside the home	
Name of Examiner:	

14.4. Appendix: Modified TWSTRS Scale

Pain Subscale	
D. Severity: Rate the severity of neck pain during the last week, on a scale of 0-10, where a score of 1 represents a minimal ache and 10 represents the most excruciating pain imaginable. Pain Severity Score = [(best+worst+2*usual)]/4 Usual (0-10) Best (0-10) Worst (0-10)	_____ _____ _____
E. Duration (rate the duration of neck pain) 0= None 1= Present <10% of the time 2= Present 10% to <25% of the time 3= Present 25% to <50% of the time 4= Present 50% to <75% of the time	

5= Present >75% of the time	
F. Disability (the degree to which pain contributes to disability) 0= No limitation or interference from pain 1= Pain is quite bothersome, but not a source of disability 2= Pain definitely interferes with some tasks, but is not a major contributor of disability 3= Pain accounts for some (less than half) but not all disability 4= Pain is a major source of difficulty with activities, separate from this, head pulling is also a source of some (less than half) disability 5= Pain is a major source of disability; without it, most impaired activities could be performed quite satisfactorily despite the head pulling	
Disability Subscale	
G. Work (occupation or housework/home management) 0= No difficulty 1= Normal work expectations with satisfactory performance at usual level of occupation, but some interference by torticollis 2= Most activities unlimited; selected activities very difficult and hampered, but still possible with satisfactory performance 3= Working at lower than usual level of occupation; most activities hampered: all possible but less than satisfactory performance in some activities 4= Unable to engage in voluntary or gainful employment; still able to perform some domestic responsibilities satisfactorily 5= Marginal or no ability to perform domestic responsibilities	
H. Activities of Daily Living (e.g., eating, dressing, hygiene [including washing, shaving, applying make-up, etc.]) 0= No difficulty with any activity 1= Activities unlimited, but some interference by torticollis 2= Most activities unlimited; selected activities very difficult and hampered, but still possible using simple tricks 3= Most activities hampered or laborious but still possible; may use extreme tricks 4= All activities impaired; some impossible or require assistance 5= Dependent on others in most self-care tasks	

I. Driving 0= No difficulty (or has never driven a car) 1= Unlimited ability to drive, but bothered by torticollis 2= Unlimited ability to drive, but requires tricks (including touching or holding face, holding head against head rest) to control torticollis 3= Can drive only short distances 4= Usually cannot drive because of torticollis 5= Unable to drive and cannot ride in car for long stretches as a passenger because of torticollis	
J. Reading 0= No difficulty 1= Unlimited ability to read in normal seated position, but bothered by torticollis 2= Unlimited ability to read in normal seated position, but requires use of tricks to control torticollis 3= Unlimited ability to read, but requires extensive measures to control torticollis or only able to read in non-seated position (e.g., lying down) 4= Limited ability to read because of torticollis despite tricks 5= Unable to read more than a few sentences because of torticollis	
K. Television 0= No difficulty 1= Unlimited ability to watch television in normal seated position, but bothered by torticollis 2= Unlimited ability to watch television in normal seated position, but requires use of tricks to control torticollis 3= Unlimited ability to watch television, but requires extensive measures to control torticollis or only able to watch in non-seated position (e.g., lying down) 4= Limited ability to watch television because of torticollis 5= Unable to watch television for more than a few minutes because of torticollis	
L. Activities Outside the Home (e.g., shopping, walking, movies, dining, and other recreational activities) 0= No difficulty 1= Unlimited activities, but bothered by torticollis 2= Unlimited activities, but requires use of simple tricks to accomplish them	

3= Only accomplishes activities when accompanied by others because of torticollis 4= Limited activities outside the home; certain activities impossible or given up due to torticollis 5= Rarely, if ever, engages in activities outside the home	
Name of Examiner:	

14.5. Appendix: CDQ-24 Scale

BECAUSE OF DYSTONIA, HOW OFTEN HAVE YOU EXPERIENCED THE FOLLOWING IN THE PAST TWO WEEKS	
Score	1. ADL: Have you had problems reading or watching TV?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	2. ADL: Has it been difficult for you to do things you like to do—for example, leisure activities?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	3. ADL: Has it been difficult for you to control the symptoms of Dystonia when you were nervous or under stress?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always

Score	4. Pain: Have you suffered from pain/a burning sensation in the face, head, or neck region?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	5. Pain: Have you been prevented from falling asleep by pain or a pulling sensation?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	6. ADL: Has it been difficult for you to do fine work with your fingers—for example, writing, threading a needle?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	7. Stigma: Have you avoided situations where many people were present—for example, social events?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	8. Stigma: Has your Dystonia made you feel uneasy in public?
0	Never

1	Occasionally
2	Sometimes
3	Often
4	Always
Score	9. Stigma: Have you felt the need to conceal your Dystonia from other people?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	10. Stigma: Have you worried about how other people react to you?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	11. Emotional Wellbeing: Have you worried about your future?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	12. Emotional Wellbeing: Have you felt afraid?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always

Score	13. Emotional Wellbeing: Have you felt down or depressed?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	14. Emotional Wellbeing: Have you been sad or on the verge of tears?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	15. Emotional Wellbeing: Have you felt annoyed or bitter?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	16. Social/Family Life: Have you felt isolated or lonely because of your Dystonia?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	17. Social/Family Life: Have you had problems with close friends or your family due to your Dystonia?
0	Never
1	Occasionally
2	Sometimes

3	Often
4	Always
Score	18. Stigma: Have you felt unsure or tense with new people?
0	Never
1	Occasionally
2	Sometimes
3	Often
4	Always
Score	19. ADL: Has it been difficult for you to keep up with the demands of your job or home life?
0	Not at all
1	Slightly
2	Moderately
3	Severely
4	Very Severely
	• Are you Employed?
	Yes
	No
Score	20. ADL: Have you experienced difficulty as a motorist or pedestrian?
0	Not at all
1	Slightly
2	Moderately
3	Severely
4	Very Severely
Score	21. Pain: Have you felt hindered by pain/a burning sensation in the face, head or neck region?
0	Not at all
1	Slightly
2	Moderately

3	Severely
4	Very Severely
Score	22. Stigma: Have you felt you didn't look so good?
0	Not at all
1	Slightly
2	Moderately
3	Severely
4	Very Severely
Score	23. Social/Family Life: Has your Dystonia had a negative effect on your family life?
0	Not at all
1	Slightly
2	Moderately
3	Severely
4	Very Severely
Score	24. Social/Family Life: Has your Dystonia negatively affected the relationship with your partner?
0	Not at all
1	Slightly
2	Moderately
3	Severely
4	Very Severely
	• Do you have a Partner?
	Yes
	No

14.6. Appendix: CGI-S and CGI-C Scales

CGI-S: Severity of Illness	
Score	Considering your total clinical experience with this particular population, how ill is the patient at this time?
1	Normal, not at all ill
2	Borderline ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients
CGI-C: Global Improvement	
Score	Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment. Compared to his/her condition at inclusion in the project, how much has he (she) changed?
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

14.7. Appendix: PGI-S and PGI-C Scales

PGI-S: Severity of Illness	
Score	Considering all of the ways your cervical dystonia affects you, how would you describe the overall severity at this time?

1	Not Present
2	Very Mild
3	Mild
4	Moderate
5	Moderately Severe
6	Severe
7	Extremely Severe
PGI-C: Global Change	
Score	Compared to your condition at baseline, your [average] condition has...?
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

14.8. Appendix: TSQM Scale

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are being asked to assess. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please select the response that most closely corresponds to your own experiences.	
Score	1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
1	Extremely Dissatisfied
2	Very Dissatisfied
3	Dissatisfied
4	Somewhat Satisfied
5	Satisfied

6	Very Satisfied
7	Extremely Satisfied
Score	2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
1	Extremely Dissatisfied
2	Very Dissatisfied
3	Dissatisfied
4	Somewhat Satisfied
5	Satisfied
6	Very Satisfied
7	Extremely Satisfied
Score	3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
1	Extremely Dissatisfied
2	Very Dissatisfied
3	Dissatisfied
4	Somewhat Satisfied
5	Satisfied
6	Very Satisfied
7	Extremely Satisfied
Score	4. As a result of taking this medication, do you experience any side effects at all?
0	No (Skip to Question 9)
1	Yes
Score	5. How bothersome are the side effects of the medication you take to treat your condition?
1	Extremely Bothersome
2	Very Bothersome
3	Somewhat Bothersome
4	A little Bothersome

5	Not at all Bothersome
Score	6. To what extent do the side effects interfere with your <u>physical</u> health and ability to function (i.e., strength, energy levels, etc.)?
1	A Great Deal
2	Quite a Bit
3	Somewhat
4	Minimally
5	Not At All
Score	7. To what extent do the side effects interfere with your <u>mental</u> function (i.e., ability to think clearly, stay awake, etc.)?
1	A Great Deal
2	Quite a Bit
3	Somewhat
4	Minimally
5	Not At All
Score	8. To what degree have medication side effects affected your overall satisfaction with the medication?
1	A Great Deal
2	Quite a Bit
3	Somewhat
4	Minimally
5	Not At All
Score	9. How easy or difficult is it to use the medication in its current form?
1	Extremely Difficult
2	Very Difficult
3	Difficult
4	Somewhat Easy
5	Easy
6	Very Easy

7	Extremely Easy
Score	10. How easy or difficult is it to plan when you will use the medication each time?
1	Extremely Difficult
2	Very Difficult
3	Difficult
4	Somewhat Easy
5	Easy
6	Very Easy
7	Extremely Easy
Score	11. How convenient or inconvenient is it to take the medication as instructed?
1	Extremely Inconvenient
2	Very Inconvenient
3	Inconvenient
4	Somewhat Convenient
5	Convenient
6	Very Convenient
7	Extremely Convenient
Score	12. Overall, how confident are you that taking this medication is a good thing for you?
1	Not at all Confident
2	A Little Confident
3	Somewhat Confident
4	Very Confident
5	Extremely Confident
Score	13. How certain are you that the good things about your medication outweigh the bad things?
1	Not at All Certain
2	A Little Certain
3	Somewhat Certain

4	Very Certain
5	Extremely Certain
Score	14. Taking all things into account, how satisfied or dissatisfied are you with this medication?
1	Extremely Dissatisfied
2	Very Dissatisfied
3	Dissatisfied
4	Somewhat Satisfied
5	Satisfied
6	Very Satisfied
7	Extremely Satisfied

14.9. Appendix: Overview of Statistical Methods and Sensitivity Analysis for Efficacy Endpoints

Overview of Statistical Methods and Sensitivity Analysis for Efficacy Endpoints

Estimand Label	Estimand Description	Analysis Set	Main Estimation	Analysis Model/Method	Sensitivity Analyses
Estimand 1a (Primary)	Difference (MTR-601– placebo) of mean change from baseline in TWSTRS at the end of Week 4 in patients with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications.	FAS	To estimate effect irrespective of treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. While alive strategy is used to reflect effect of treatment while alive.	MMRM Model estimates with standard error (SE) for intervention effect at Week 4, the 95% CI of the effect, and the p-value derived from the model.	ANCOVA model with MI using retrieved dropouts. In an event of a convergence issue, copy-reference MI model will be used for imputation.
Estimand 1b (Supplementary)	Difference (MTR-601– placebo) of mean change from baseline in TWSTRS at the end of Week 4 in patients with cervical dystonia as if there were no treatment discontinuation, dose modification, or use of prohibited concomitant medications.	FAS	To estimate effect as if there were no treatment discontinuation for any reason, dose modification, or use of prohibited concomitant medication. While alive strategy is used to reflect effect of treatment while alive.	As above	Not Applicable (NA)
Estimand 2	Difference (MTR-601– placebo) of mean change from baseline in TWSTRS severity, pain and disability scores at the end of Week 4 in patients with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications.	FAS	Same as Estimand 1a	As above	NA

Overview of Statistical Methods and Sensitivity Analysis for Efficacy Endpoints

Estimand Label	Estimand Description	Analysis Set	Main Estimation	Analysis Model/Method	Sensitivity Analyses
Estimand 3	Difference (MTR-601– placebo) of mean change from baseline in TWSTRS overall, severity, pain and disability scores at the end of Week 2 in patients with cervical dystonia regardless of treatment discontinuation, dose modification, or use of prohibited concomitant medications.	FAS	Same as Estimand 1a	As above	NA

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Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
Witness Events	Signature	Timestamp
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Envelope Summary Events	Status	Timestamps
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Signing Complete	Security Checked	22 January 2026 16:01
Completed	Security Checked	22 January 2026 16:01
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