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Statistical Analysis Plan

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An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity (Study OS3440-3005).

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STATISTICAL ANALYSIS PLAN

Protocol Title:	An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity (Study OS440-3005)
Protocol Number:	OS440-3005
Phase:	Phase 3
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1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation	Definition
ADaM	Analysis data Model
AE	Adverse event
AERT	Arbaclofen extended-release tablets
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case report form
C-SSRS	Columbia–Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRT	Interactive Response Technology (system)
mAS	Modified Ashworth Scale
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple Sclerosis
PGIC	Patient Global Impression of Change
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNmAS-MAL	Total Numeric-Transformed Modified Ashworth Score – Most Affected Limb
TNmAS-TL	Total Numeric-Transformed Modified Ashworth Score – Total Limbs
USP	Urinary Symptom Profile - USP© questionnaire
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for Osmotica Pharmaceutical's Protocol OS440-3005 (*An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity*).

Reference materials for this statistical plan includes the protocol OS440-3005 (CLN.OS440-3005.PR.A01Dated: 03 OCT 2017).

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to locking of the study database.

For the reasons stated here, the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

3.2. Purpose of Analyses

The purposes of the planned analyses described in this SAP are to assess the safety and efficacy of oral arbaclofen extended-release tablets (AERT) in MS subjects with spasticity. Results from the analyses completed will be included in the final clinical study report for Study OS440-3005, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report but will be fully documented in the document containing the additional analyses.

3.3. Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan are consistent with the analyses described in the study protocol.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of AERT in subjects with spasticity due to MS.

4.1.2. Secondary Objectives

The secondary objectives are to:

- Assess the Patient Global Impression of Change (PGIC) over 1 year.
- Assess the Total Numeric-transformed modified Ashworth Scale score of the most affected limb (TNmAS-MAL) over 1 year.
- Assess the Expanded Disability Status Scale (EDSS) over 1 year.

4.2. Study Endpoints

4.2.1. Safety Endpoints

Safety endpoints include the following:

- Adverse events
- Vital signs
- Clinical laboratory tests
- 12-lead electrocardiograms (ECGs)
- Urinary Symptom Profile - USP© questionnaire (USP)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

4.2.2. Efficacy Endpoints

Efficacy endpoints include the following:

- Patient Global Impression of Change (PGIC)
- Total Numeric-Transformed Modified Ashworth Score – Most Affected Limb (TNmAS-MAL)
- Total Numeric-Transformed Modified Ashworth Score – Total Limbs (TNmAS-TL)
- Expanded Disability Status Scale (EDSS)

5. STUDY METHODS

5.1. General Study Design and Plan

As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

This is a multicenter, open-label, long-term extension study to evaluate the safety and tolerability of oral AERT in subjects with spasticity due to MS. Subjects from the double-blind study (Study OS440-3004) may rollover into this open-label extension study, as well as de novo subjects, provided that all inclusion and none of the exclusion criteria are met.

Eligible de novo subjects will undergo an at least 21-day washout period for withdrawal of all medications used for anti-spasticity and/or muscle relaxation prior to enrolling in this open-label study. There will be a 9-day titration period, then a 52-week maintenance period, followed by a 2-week taper period.

Figure 1 presents the timeline diagram for the study. Figure 2 presents the open-label dosing regimen flowchart, including titration and taper doses, to be used during the study. Once the subject has reached the maintenance dose, they will remain on that dose for approximately 1 year. The maintenance dose will be the highest tolerated dose not exceeding 80 arbaclofen mg per day.

The schedule of assessments is presented in Table 1.

Figure 1 Timeline Diagram

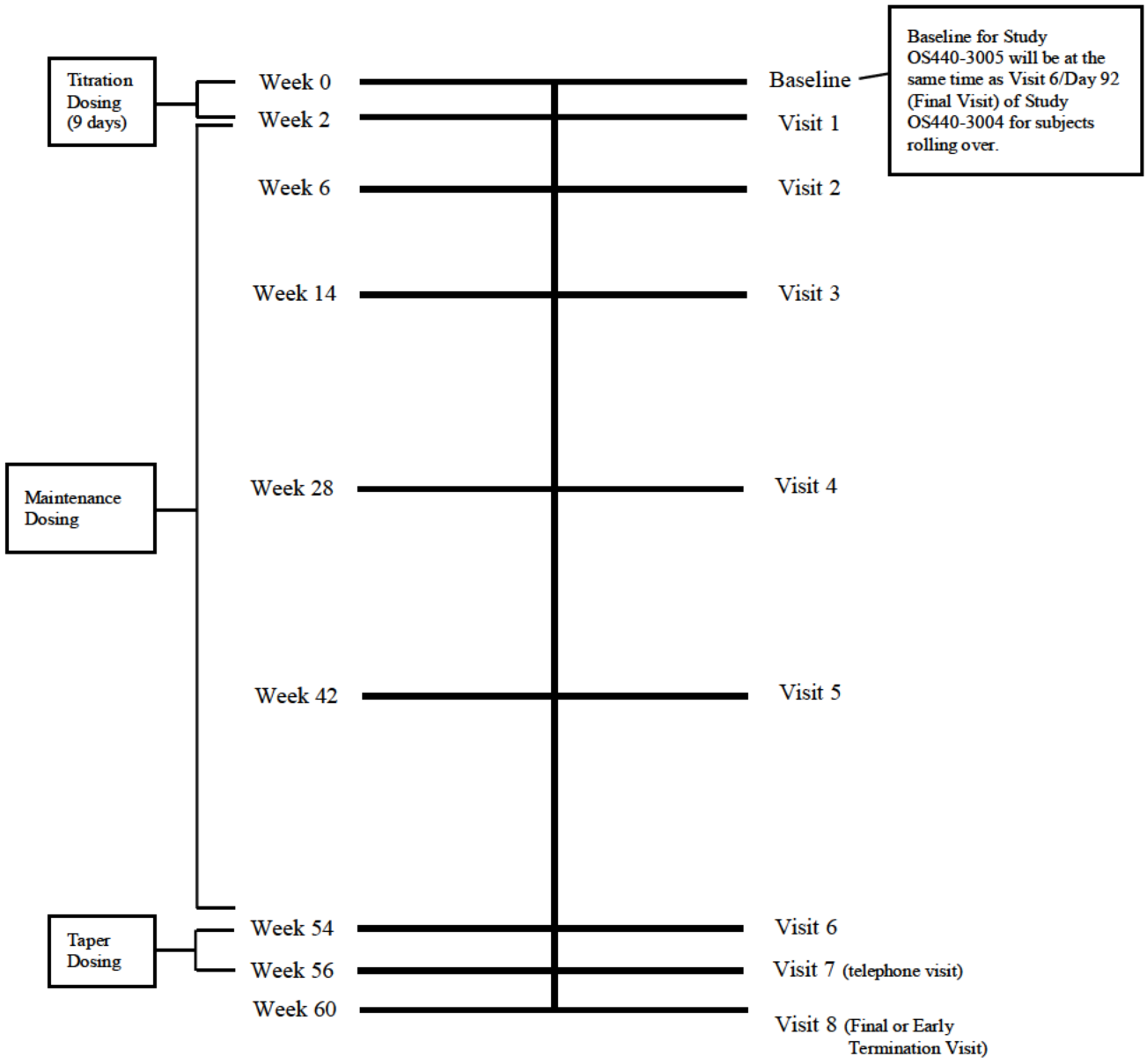
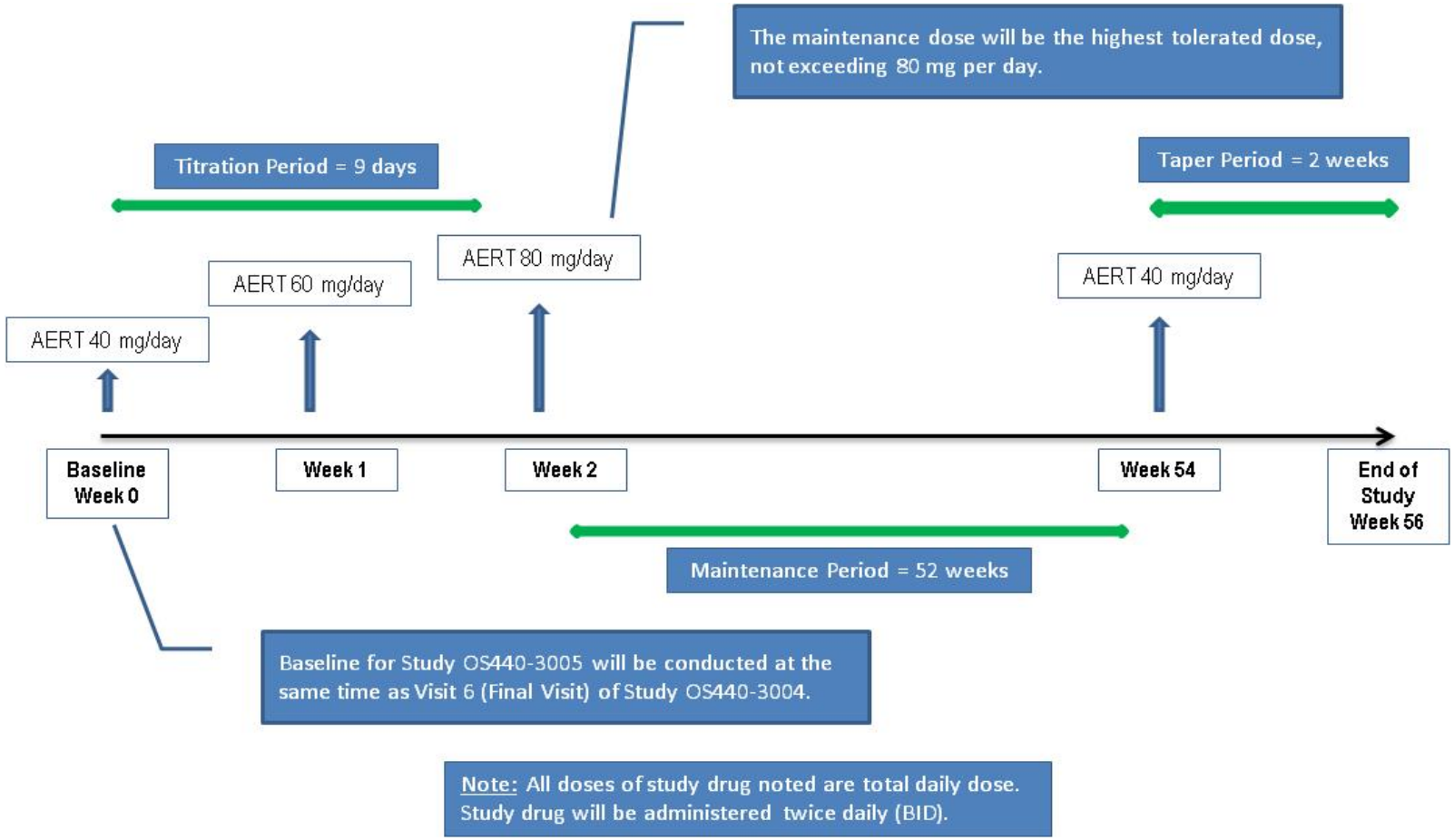


Figure 2 Flowchart of Open-Label Dosing Regimen



At the end of treatment, a 2-week taper period will take place from Weeks 54 to 56. Subjects who discontinue early should also follow the 2-week taper period.

Table 1 Schedule of Assessments

Assessment or Procedure	Baseline[1]	Visits							Final Visit[2]
Study Visit	**(V6 of prior DB Study)**	**1**	**2**	**3**	**4**	**5**	**6**	**7 (telephone visit)**	**8**
Study Week	**0 (±3 days)**	**2 (±3 days)**	**6 (±5 days)**	**14 (±5 days)**	**28 (±5 days)**	**42 (±5 days)**	**54 (±3 days)**	**56 (±5 days)**	**60 (±3 days)**
Written informed consent	X								
Inclusion and exclusion criteria	X								
Withdrawal anti-spasticity medication	X								
Assign enrollment number	X								
Demography	X								
Medical/surgical history	X								
Physical examination	X								
Height	X								
Weight	X				X				X
Vital signs[3]	X	X	X	X	X	X	X		X
Hematology/serum chemistry/urinalysis	X		X	X	X	X	X		X
Electrocardiogram	X				X				X
Pregnancy test[4]	X	X	X	X	X	X	X		X
C-SSRS	X	X	X	X	X	X	X		X
TNmAS-MAL[5]	X				X				X
EDSS	X				X				X
PGIC[6]	X				X				X
USP© questionnaire	X	X	X	X	X	X	X		X
Dispense study medication	X	X	X	X	X	X	X[7]		
Collect unused study medication		X	X	X	X	X	X		X
Adverse event assessment	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X
Schedule/confirm next study visit	X	X	X	X	X	X	X	X	

C-SSRS = Columbia–Suicide Severity Rating Scale; DB = double-blind; EDSS = Expanded Disability Status Scale; FV = final visit; PGIC = Patient Global Impression of Change; TNmAS-MAL = Total Numeric-transformed modified Ashworth Scale score of the most affected limb; USP = Urinary Symptom Profile.

(footnotes on next page)

Table 1 - Footnotes:

1. Baseline for the study will be conducted at the same time as Visit 6/Day 92 (Final Visit) of Study OS440-3004 for subjects willing to continue into this study. All assessments performed at Visit 6/Day 92 (Final Visit) of Study OS440-3004 should not be repeated but should be recorded as the same assessments at Baseline for this study.

   Note: For *de novo* subjects being considered for enrollment, a Screening visit (not shown in Table 1) should occur a maximum of 21 days prior to Baseline to allow for any concomitant medication wash-out required for Inclusion Criterion 6. For *de novo* subjects, the first three procedures listed under Baseline (ie, informed consent, inclusion/exclusion criteria, and withdrawal of anti-spasticity medication) will be done at this Screening visit, as well as a serum pregnancy test (see footnote 4 below). All other baseline assessments and procedures listed will be performed at the Baseline visit for *de novo* subjects.

2. If a subject prematurely withdraws from the study, the subject should taper from study medication as described in Protocol Section 7.1 and all evaluations described under Visit 8/Week 60 (Final Visit) must be performed.

3. Vital signs will be measured with the subject in a supine position and in a standing position 3 minutes after the supine assessment is completed. Body temperature and respiratory rate will be measured only during the supine assessment.

4. For *de novo* subjects, premenopausal women of childbearing potential must have a negative serum pregnancy test within 21 days before Baseline. Urine pregnancy testing will be performed for all female subjects at the other visits as noted.

5. The TNmAS-MAL assessment will be performed prior to any scheduled lab draws. The most affected limb will be determined by the investigator.

6. The PGIC will not be done at Baseline for *de novo* subjects.

7. At the end of treatment, a 2-week taper period will take place from Weeks 54 to 56. Subjects who discontinue early should also follow the 2-week taper period.

5.2. Randomization and Blinding

Not applicable, this is an open-label, non-randomized study.

5.3. Analysis Variables

Variables to be analyzed include demographics and baseline characteristics, safety variables (adverse events, vital signs, clinical laboratory investigations, ECGs, USP questionnaire, and C-SSRS), and efficacy variables (PGIC, TNmAS-MAL, TNmAS-TL, and EDSS). See Section 8 of the protocol for further details on the efficacy variables. Derived variables from study endpoints are described with the sections describing the analyses for these endpoints.

6. SAMPLE SIZE

In total, approximately 300 subjects are to be enrolled in this study (ie, both rollover and de novo subjects). It is anticipated that approximately 50% of subjects randomized into the double-blind study (Study OS440-3004) may rollover into this open-label study. In the US only, up to 50 subjects may enroll into Study OS440-3005 without rolling over from Study OS440-3004.

The number of subjects at each site will be determined primarily by the rate of recruitment in Study OSS440-3004. No statistical rationale for subject number is provided.

The sponsor has previously completed a 1-year, open-label safety study (Study OS440-3003 using the 40-mg per day dose of arbaclofen. In Study OS440-3003 a total of 148 subjects were treated for 12 months. Study OS440-3005 is designed to enrich the existing safety database and provide long-term safety and tolerability data at the maximum daily dose of 80 mg/day. Target recruitment for Study OS440-3005 includes at least 100 subjects treated at 6 months and 50 subjects treated for 1 year at 80-mg per day.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

There will be two (2) analysis populations defined for this study.

7.1.1. Screened Population (SCREEN)

Subjects who provide informed consent will be members of the screening population. The screening population will include the total number of subjects who were considered for this study (rollover and *de novo*), regardless of participation.

7.1.2. Safety Population (SP)

Includes all subjects who receive at least one dose of open-label study treatment and have at least one post-dose visit. This population will be used for all safety and efficacy analyses.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

No covariates are planned for this study.

7.2.2. Planned Subgroups

No subgroups are planned for this study.

7.3. Management of Analysis Data

7.3.1. Data Handling

Unscheduled or repeated laboratory results will not be analyzed for the summary of continuous values but will be included in the laboratory shift tables as follows. Unscheduled tests will be included with the time of the nearest regularly scheduled test. If there is a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with low or high results) will be used. Repeated tests will be included only if they reflect abnormal (low or high) results and the corresponding original results are normal. All laboratory values, for all visits, will be provided in by subject listings.

7.3.2. Missing Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the case report form (CRF) will be included in data listings that will accompany the clinical study report.

7.3.2.1. Handling of Missing Date Values

<u>Partial or Missing Dates</u>

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then:

i) If the year matches the first dose date year, then impute the month and day of the first dose date.
ii) Otherwise, assign 'January.'

3) If the day is unknown, then:
i) If the month and year match the first dose date month and year, then impute the day of the first dose date.
ii) Otherwise, assign the first day of the month.

B. Stop Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2) If the month is unknown, then assign 'December.'
3) If the day is unknown, then assign the last day of the month.

7.3.2.2. Imputation Methods

Observed cases, without imputation, will be used for of analyses.

If the relationship of an AE is missing, it will be considered treatment-related. Missing AE severity will be coded as severe.

7.3.3. Handling of Early Termination Visit Information

If a subject is terminated early from this study the early termination visit data will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

7.3.4. Pooling of Study Centers

No pooling of study centers is planned for this study.

7.3.5. Coding Conventions for Events and Medications

All adverse events, and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1) system for reporting (preferred term and body system). Prior and concomitant medications will be coded using WHO-DD (Drug Dictionary) (Version September 2017).

7.3.6. Analysis Software

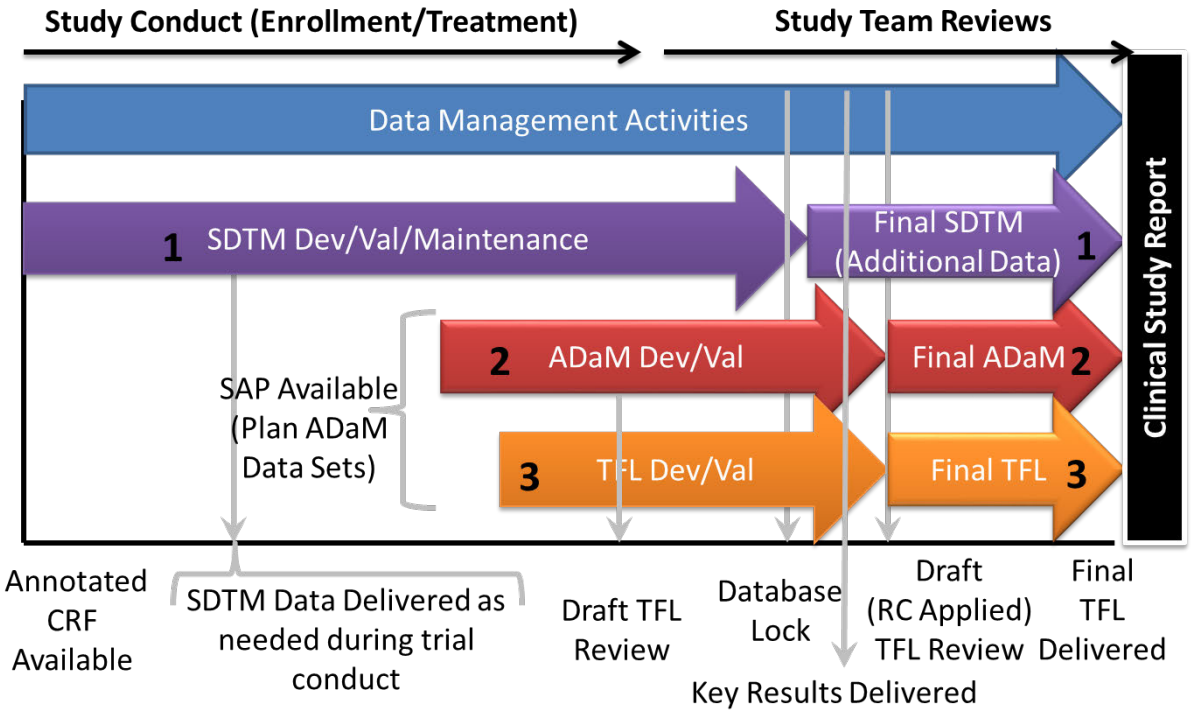
Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

7.3.7. Study Data

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. All planned analyses will be performed using the ADaM data sets developed for this study.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 3.

Figure 3 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, Validation, and Maintenance of SDTM Domains
2. Development and Validation of Analysis Data Sets (ADaM), with input source the appropriate SDTM domains.
3. Development and Validation of Tables, Figures, and Listings (TFL), with input data source the analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

No statistical tests will be performed in this study.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be tabulated. For categorical variables, the counts and proportions of each value will be tabulated. Expansion of descriptive table categories may occur if such elaborations are thought to be useful.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. The standard deviation / standard error will be displayed to two levels of precision greater than the data collected.

Change from baseline scores will be calculated as the post-baseline measurement minus the baseline value.

Unless otherwise specified, all tables will be presented by Modal Dose of 40 mg, 60 mg, 80 mg, and Overall group.

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or figures but will be included in the data listings.

7.4.2. Interim Analyses and Data Monitoring

No formal interim analysis is planned for this study.

A Data Safety Monitoring Board (DSMB) will oversee study subject safety with respect to AEs and clinically important lab values. DSMB members will be independent of the Sponsor, study sites, and the managing vendors, and will have no other role in the trial. DSMB meetings for Study OS440-3005 will be scheduled after approximately 25% subjects have been randomized or 300 AEs (whichever comes first), 50% subjects have been randomized or 600 AEs (whichever comes first), 75% subjects have been randomized or 900 AEs (whichever comes first) and 100% of subjects have been randomized. The DSMB Chairman will be responsible for determining a time for unscheduled meetings

7.4.3. Multiple Testing Procedures

Not applicable.

8. SUMMARY OF STUDY DATA

8.1. Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects screened (rollover and de novo) and in the safety population. All percentages will be based on the number of subjects screened.

End of trial information will also be summarized in this table, including the number of subjects completing the study and the number of subjects who prematurely discontinued the study with reasons for withdrawal. All percentages will be based on the number of subjects screened.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

8.2. Protocol Deviations

All protocol deviations will be presented in a data listing. A summary table will also be generated based on the classification of protocol deviations.

8.3. Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively. Individual subject demographics and baseline characteristics will be provided in listings.

8.4. Medical and Surgical History

Medical and surgical history will be coded using the MedDRA Version 20.1.

Subject medical and surgical history data including specific details will be presented in a listing.

8.5. Prior and Concurrent Medications

The number and percentages of all concomitant medications will be summarized, Anatomical Therapeutic Chemical (ATC) level 4 and PT. The total number of concomitant medications and the number and percentages of subjects with at least 1 concomitant medication will be summarized.

The number and percentages of all prior medications will be summarized similarly to concomitant medications in a separate table.

A concomitant medication is defined as any medication taken on or after the day of first dose of study drug. The prior medications are defined as any medication that starts and ends prior to the first dose of study drug.

8.6. Treatment Compliance

The total number of days at each unique dose level and overall will be summarized.

Dosing information, including date of administration, and days at each unique dose level will be listed by subject.

9. EFFICACY ANALYSES

9.1. Efficacy Endpoints

Efficacy endpoints include the following:

- Patient Global Impression of Change (PGIC)
- Total Numeric-Transformed Modified Ashworth Score – Most Affected Limb (TNmAS-MAL)
- Total Numeric-Transformed Modified Ashworth Score – Total Limbs (TNmAS-TL)
- Expanded Disability Status Scale (EDSS)

9.2. Efficacy Analyses

PGIC categories will be summarized by frequencies and percentages by study visit. PGIC will also be summarized using descriptive statistics by study visit.

TNmAS-MAL, TNmAS-TL, and EDSS will be summarized descriptively by study visit in terms of actual values and change from baseline values. In addition to this change from baseline (from Visit 6/ET in OS440-3004), the change from baseline in Study OS440-3004 will be summarized for TNmAS-MAL and TNmAS-TL.

10. SAFETY ANALYSES

10.1. Adverse Events

The number and percent of subjects with any treatment-emergent adverse events (TEAEs) will be displayed by system organ class and preferred term (MedDRA Version 20.1). Within each preferred term, subjects will be counted only once if they had more than one event reported during the treatment period.

TEAEs will also be summarized by greatest reported severity for each event preferred term. Counts indicate subjects reporting one or more TEAEs that map to the severity grade classification for each preferred term. At each level of summarization (system organ class or event preferred term) subjects are only counted once and the worst severity case of repeated instances of the same TEAE will be used in tabulations. TEAEs will also be summarized by strongest investigator assessment of relationship to study drug in a similar manner.

In addition to the above described analyses, specific AE summaries will be presented under the following conditions:

- TEAEs by SOC/PT will be presented by modal dose within period (titration/dose response, maintenance, and taper period).

- TEAEs by SOC/PT will be presented by dose the subject was on at time of event within period (titration/dose response, maintenance, and taper period).

- All AE summaries will be presented by dose the subject was on at time of event.

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any AE with onset or worsening on or after the first dose of study drug up until last dose of study drug.

Treatment emergent summarization will be characterized by serious or not, the severity and the relationship with the study drug. A conservative approach will be taken to assess the relationship of an AE to study drug; if the relationship of an event is missing, it will be considered treatment-related. Missing severity will be coded as severe.

All TEAEs will be listed individually by subject. In addition, a separate listing will be produced for AEs that are not treatment-emergent.

10.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

10.2.1. Deaths

All deaths, regardless of causality, will be provided in listings and written clinical narratives.

10.2.2. Serious Adverse Events

The number and percent of subjects with Treatment Emergent Serious Adverse Event (TESAE) will be displayed by system organ class and preferred term, and relationship to study drug. Within each preferred term, subjects will be counted only once if they had more than one TESAE event reported during the treatment period.

Clinical narratives for each TESAE observed will be written to include important data and safety findings related to the individual TESAE and included in the final clinical study report.

10.2.3. Adverse Events Leading to Discontinuation of Study Drug

The number and percent of subjects with TEAE's leading to discontinuation, or interruption, of study drug will be displayed by system organ class and preferred term. Within each preferred term, subjects will be counted only once if they had more than one TEAE leading to discontinuation, or interruption, of study drug reported during the treatment period.

A listing will be produced for all subjects who reported serious TEAEs or who discontinued study drug due to TEAEs.

10.3. Clinical Laboratory Evaluations

Clinical Laboratory results will be summarized descriptively by time point for the observed value as well as for the change from baseline value. In addition, laboratory shift tables will be provided for all laboratory parameters where low/normal/high or abnormal/normal status can be ascertained. Listings of individual laboratory parameters by visit with normal ranges and abnormality assessments will also be completed by subject.

10.4. Vital Signs

Vital sign results will be summarized descriptively by time point for the observed value as well as for the change from baseline value. All vital sign data by subject will be presented in a listing. Unscheduled visit results will not be summarized but will be included in subject data listings.

10.5. Physical Examinations

Physical examinations are conducted at baseline. A by subject listing will be completed to display all baseline physical examination information, as well as any optional PE information collected.

10.6. Other Safety Measures

C-SSRS results will be presented in subject data listings.

USP summary scores (stress urinary incontinence score, overactive bladder score, and low stream score) will be summarized descriptively by time point for the observed value as well as for the change from baseline value. All USP data (including the 10 individual questions) will be presented in listings.

ECG parameters will be summarized descriptively by time point for the observed value as well as for the change from baseline value. All ECG data will be presented in listings.

No other safety analyses have been prospectively defined. If, however, after study results are reviewed, or the DSMB or Sponsor recommend additional safety parameters or analyses be completed, they will be fully described and documented in the final clinical study report. The SAP does not need to be amended to complete any other safety measures identified as post-hoc.

11 REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations

11.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in presented in color with treatment groups distinguished by different symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g.,μ,α,β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO 8601 format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.
- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the Table, Listing, or Graph

status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.

- All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

- Study Number (Study OS440-3005) will be on every table, figure, or data listing display.

11.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "Population: <name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., FAS Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include: N, mean, SD, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of percent that results in 0% is to be presented as a blank.
- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software version) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000.

12 REVISION HISTORY

Changes from version SAP.00: The SAP was revised and amended to remove the 30 day window for the derivation of treatment emergent adverse events. Adverse events will now be counted as treatment emergent up until the last dose date.

Changes from version SAP.01: The SAP was revised and amended to add additional Adverse event analyses: All AE analyses by dose the subject was on at time of event; TEAEs by SOC/PT by modal dose and period (titration/dose response, maintenance, and taper period); TEAEs by SOC/PT analyses by dose the subject was on at time of event and period (titration/dose response, maintenance, and taper period).

For TNmAS-MAL and TNmAS-TL, the baseline from OS440-3004 will be included as a separate analysis to the planned analyses using the baseline of Visit 6/ET result from Study OS440-3004.

For dose exposure, the total days at each particular dose level have been added to the subject listing and a new summary table counting the total days at each dose level and overall has been included.

For all tables modal dose categories have been changed from < 80 and = 80 mg to modal dose categories of 40 mg, 60 mg, and 80 mg.