

# STATISTICAL ANALYSIS PLAN

**Official Title:**

A Phase 2, double-blind, placebo-controlled, parallel-group study followed by an open-label, parallel group extension part to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and potential efficacy of multiple doses of ONO-2808 in patients with Multiple System Atrophy (MSA)

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# **Statistical Analysis Plan**

**A Phase 2, double-blind, placebo-controlled, parallel-group study followed by an open-label, parallel group extension part to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and potential efficacy of multiple doses of ONO-2808 in patients with Multiple System Atrophy (MSA)**

**(Protocol Number ONO-2808-03)**

**ONO PHARMACEUTICAL CO., LTD**

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### Statistical Analysis Plan - Approval Signature Page

Protocol: ONO-2808-03

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## TABLE OF CONTENTS

|                                                         |    |
|---------------------------------------------------------|----|
| LIST OF TABLES .....                                    | 7  |
| LIST OF APPENDICES .....                                | 8  |
| LIST OF ABBREVIATIONS.....                              | 9  |
| 1 INTRODUCTION .....                                    | 14 |
| 2 STUDY SYNOPSIS .....                                  | 15 |
| 2.1 Study Overview .....                                | 15 |
| 2.2 Study Objectives and Endpoints .....                | 16 |
| 2.3 Randomization and Blinding .....                    | 19 |
| 2.4 Duration of Subject Participation .....             | 20 |
| 3 HYPOTHESIS TESTING AND SIGNIFICANCE LEVEL.....        | 21 |
| 3.1 Multiplicity Adjustment.....                        | 21 |
| 4 TIMING OF PLANNED ANALYSIS.....                       | 22 |
| 5 SAMPLE SIZE .....                                     | 23 |
| 5.1 Sample Size by Region.....                          | 23 |
| 5.2 Sample Size re-estimation .....                     | 23 |
| 6 ANALYSIS SETS .....                                   | 24 |
| 7 GENERAL STATISTICAL CONSIDERATIONS.....               | 25 |
| 7.1 Software to be used in Analyses .....               | 25 |
| 7.2 Output Conventions.....                             | 25 |
| 7.3 General Data Handling Conventions.....              | 26 |
| 7.4 Re-screened Subjects.....                           | 26 |
| 7.5 Baseline definition.....                            | 26 |
| 7.6 Study Day.....                                      | 26 |
| 7.7 Handling Rules for Time Points.....                 | 27 |
| 7.8 Multi-center Studies .....                          | 30 |
| 7.9 Definition of covariates and subgroup factors ..... | 30 |
| 7.9.1 Covariates.....                                   | 31 |
| 7.9.2 Subgroup Factors.....                             | 31 |
| 8 SUMMARY OF STUDY ENDPOINTS AND ANALYSIS SETS .....    | 32 |
| 9 SUBJECT DISPOSITION .....                             | 33 |
| 10 PROTOCOL DEVIATIONS.....                             | 35 |

|        |                                                                |    |
|--------|----------------------------------------------------------------|----|
| 11     | SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS .....        | 37 |
| 12     | MEDICAL HISTORY .....                                          | 38 |
| 13     | DISEASE SPECIFIC CHARACTERISTICS .....                         | 39 |
| 14     | PRIOR AND CONCOMITANT MEDICATIONS .....                        | 40 |
| 14.1   | Analysis Items and Data Handling .....                         | 40 |
| 14.2   | Analysis Methods .....                                         | 40 |
| 15     | STUDY MEDICATION EXPOSURE/COMPLIANCE AND<br>TOLERABILITY ..... | 42 |
| 15.1   | Analysis Items and Data Handling .....                         | 42 |
| 15.2   | Analysis Methods .....                                         | 43 |
| 16     | EFFICACY .....                                                 | 44 |
| 17     | SAFETY .....                                                   | 45 |
| 17.1   | Dose Limiting Toxicities .....                                 | 45 |
| 17.2   | Adverse Events and Deaths .....                                | 45 |
| 17.2.1 | Analysis Items and Data Handling .....                         | 45 |
| 17.2.2 | Analysis Methods .....                                         | 47 |
| 17.3   | Clinical Laboratory Evaluations.....                           | 51 |
| 17.3.1 | Analysis Items and Data Handling .....                         | 51 |
| 17.3.2 | Analysis Methods .....                                         | 51 |
| 17.4   | Physical Examinations.....                                     | 54 |
| 17.4.1 | Analysis Items and Data Handling .....                         | 54 |
| 17.4.2 | Analysis Methods .....                                         | 54 |
| 17.5   | Vital Signs.....                                               | 54 |
| 17.5.1 | Analysis Items and Data Handling .....                         | 54 |
| 17.5.2 | Analysis Methods .....                                         | 55 |
| 17.6   | 12-Lead ECGs.....                                              | 55 |
| 17.6.1 | Analysis Items and Data Handling .....                         | 55 |
| 17.6.2 | Analysis Methods .....                                         | 55 |
| 17.7   | Columbia Suicide Severity Rating Scale .....                   | 56 |
| 17.7.1 | Analysis Items and Data Handling .....                         | 56 |
| 17.7.2 | Analysis Methods .....                                         | 57 |
| 18     | PHARMACOKINETICS .....                                         | 58 |
| 18.1   | Analysis Items and Data Handling .....                         | 58 |

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## LIST OF TABLES

|             |                                                         |    |
|-------------|---------------------------------------------------------|----|
| Table 2.2-1 | Study Objectives and Endpoints .....                    | 17 |
| Table 5-1   | Power for selected event rates, per treatment arm ..... | 24 |

|              |                                                                                 |    |
|--------------|---------------------------------------------------------------------------------|----|
| Table 7.2-1  | Derived variables and decimal places to display for original data.....          | 26 |
| Table 7.7-1  | Time Windows for Vital Signs (Core Part) .....                                  | 28 |
| Table 7.7-2  | Time Windows for Vital Signs (Extension Part) .....                             | 29 |
| Table 7.7-3  | Time windows for 12-ECG (Core part).....                                        | 30 |
| Table 7.7-4  | Time windows for 12-ECG (Extension part).....                                   | 30 |
| Table 7.7-5  | Time windows for subject reported outcome assessments (Core<br>part).....       | 31 |
| Table 7.7-6  | Time windows for subject reported outcome assessments<br>(Extension part) ..... | 31 |
| Table 7.7-7  | Time windows for Plasma Pharmacokinetics sampling (Core part) .....             | 31 |
| Table 7.9-1  | Covariates .....                                                                | 32 |
| Table 8-1    | Summary of Outcome Variables and Analysis Sets.....                             | 33 |
| Table 14.1-1 | Algorithm for Assigning Prior and Concomitant Medication<br>Status .....        | 41 |
| Table 17.2-1 | Algorithm for Assigning Treatment-emergent Adverse Event<br>Status .....        | 48 |

## LIST OF APPENDICES

|            |    |
|------------|----|
| APPENDIX 1 | 75 |
|------------|----|

## LIST OF ABBREVIATIONS

|            |                                                   |
|------------|---------------------------------------------------|
| AE         | Adverse Event                                     |
| AESI       | Averse Event of Special Interest                  |
| ALP        | Alkaline phosphatase                              |
| ALT        | Alanine aminotransferase                          |
| ApoM       | Apolipoprotein M                                  |
| aPTT       | Activated Partial Thromboplastic Time             |
| AST        | Aspartate aminotransferase                        |
| ATC        | Anatomical Therapeutic Chemical                   |
| ATP        | Adenosine triphosphate                            |
| β-hCG      | Urine Beta Human Chorionic Gonadotrophin          |
| BLQ        | Below the lower limit of quantification           |
| BMI        | Body Mass Index                                   |
| CI         | Confidence Interval                               |
| CKD-EPI    | Chronic Kidney Disease Epidemiology Collaboration |
| CPK        | Creatinine phosphokinase                          |
| COVID-19   | Coronavirus Disease of 2019                       |
| COA        | Clinical Outcome Assessment                       |
| CS         | Clinically Significant                            |
| ██████████ | ████████████████████████████████████████          |
| ██         | ████████████████                                  |
| CPK        | Creatine phosphokinase                            |
| CSR        | Clinical Study Report                             |
| C-SSRS     | Columbia Suicide Severity Rating Scale            |

|        |                                                |
|--------|------------------------------------------------|
| CTCAE  | Common Terminology Criteria for Adverse Events |
| CT     | Computed Tomography                            |
| ██████ | ████████████████████                           |
| ███    | ██████████                                     |
| DBL    | Direct bilirubin                               |
| DDI    | Drug-Drug Interaction                          |
| DILI   | Drug-induced Liver Injury                      |
| DLB    | Dementia with Lewy Bodies                      |
| DSUR   | Development Safety Update Report               |
| DTI    | Diffusion Tensor Imaging                       |
| ECG    | Electrocardiogram                              |
| eCRF   | Electronic Case Report Form                    |
| EOT    | End of Treatment                               |
| ET     | Early Termination                              |
| FAS    | Full Analysis Set                              |
| FSH    | Follicle-Stimulating Hormone                   |
| ███    | ████████████████                               |
| ███    | ██████████                                     |
| ██████ | ██████████████████                             |
| GGT    | Gamma-glutamyl transferase                     |
| ██████ | ██████████████████                             |
| HBsAg  | Hepatitis B surface antigen                    |
| HCV    | Hepatitis C virus                              |
| ICF    | Informed Consent Form                          |

|        |                                              |
|--------|----------------------------------------------|
| ICH    | The International Council for Harmonisation  |
| IDMC   | Independent Data Monitoring Committee        |
| ██████ | ████████████████████████████████████████     |
| IEC    | Independent Ethics Committee                 |
| IMP    | Investigational Medicinal Product            |
| INR    | International Normalized Ratio               |
| IPD    | Important Protocol Deviation                 |
| IP     | Investigational Product                      |
| █      | ████████████████████                         |
| IRB    | Institutional Review Board                   |
| ████   | ████████████████████████████████             |
| ITT    | Intention-To-Treat                           |
| IVRS   | Interactive Voice Response System            |
| IWRS   | Interactive Web Response System              |
| LDH    | Lactate Dehydrogenase                        |
| LFT    | Liver Function Test                          |
| █      | ████████████████                             |
| ████   | ████████████████████████████████             |
| ████   | ████████████████████████████                 |
| MCH    | Mean Corpuscular Hemoglobin                  |
| MCV    | Mean Corpuscular Volume                      |
| MDS    | Movement Disorder Society                    |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI    | Magnetic Resonance Imaging                   |

|        |                                                   |
|--------|---------------------------------------------------|
| MSA    | Multiple System Atrophy                           |
| MSA-P  | Multiple System Atrophy with Parkinsonian Variant |
| MSA-C  | Multiple System Atrophy with Cerebellar Variant   |
| ██████ | ████████████████████████████████████████          |
| ████   | ████████████████████                              |
| NC     | Not Calculated                                    |
| NCS    | Not Clinically Significant                        |
| PD     | Pharmacodynamic                                   |
| PK     | Pharmacokinetic                                   |
| PRO    | Patient Reported Outcome                          |
| PT     | Preferred Term                                    |
| QD     | Once Daily                                        |
| QTcB   | QT Interval Corrected using Bazett's formula      |
| QTcF   | QT Interval Corrected using Fridericia's formula  |
| RDI    | Relative Dose Intensity                           |
| S1P    | Sphingosine-1-phosphate                           |
| S1PR5  | Small Molecule Sphingosine-1-Phosphate Receptor-5 |
| ████   | ████████████████████                              |
| SAE    | Serious Adverse Event                             |
| SAF    | Safety Analysis Set                               |
| SAP    | Statistical Analysis Plan                         |
| SAS    | Statistical Analysis System                       |
| SD     | Standard Deviation                                |
| ██████ | ████████████████████████████████████████          |

|         |                                               |
|---------|-----------------------------------------------|
| SGPT    | Serum Glutamic-Pyruvic Transaminase           |
| SIB     | Suicidal Ideation and Behavior                |
| SI      | International System                          |
| SoA     | Schedule of Activities                        |
| SOC     | System Organ Class                            |
| SRC     | Study Review Committee                        |
| TBL     | Total bilirubin                               |
| TEAE    | Treatment-Emergent Adverse Event              |
| TESAE   | Treatment-emergent Serious Adverse Event      |
| ULN     | Upper Limit of Normal                         |
| UMSARS  | Unified Multiple System Atrophy Rating Scale  |
| US      | United States                                 |
| WHO-DRL | World Health Organization Drug Reference List |
| WOCBP   | Woman of Childbearing Potential               |
| ULN     | Upper Limit of Normal                         |
| ■       | ■                                             |

## 1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a description of the statistical methodology to be implemented for data analysis of the study described in Protocol ONO-2808-03 (Version 5.0; 21Jun2024) and the corresponding case report form (CRF) (Version 9.0, 30May2025). It also covers any later amendments to the protocol that may be produced that have no material effect on the statistical analysis (refer to relevant file note(s), if applicable). However, if circumstances arise during the study such that more appropriate analytical procedures or methodologies become available/are warranted, or if there is a protocol amendment which necessitates changes to the SAP, then this document will be revised. Any deviations from this analysis plan will be substantiated by sound rationale and will be documented in the clinical study report (CSR). Otherwise, the CSR will consider all the information defined in this SAP.

This SAP is being written with consideration of the recommendations outlined in the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials<sup>1</sup>” and the most recent ICH E3 Guideline entitled, “Guidance for Industry: Structure and Content of Clinical Study Reports<sup>2</sup>.”

All planned analyses identified in this SAP will be performed by [REDACTED] unless otherwise stated.

## 2 STUDY SYNOPSIS

The following Sections 2.1 and 2.2 represent a summary of what can be found in the protocol.

### 2.1 Study Overview

Study ONO-2808-03 is a Phase 2, double-blind, parallel-group, placebo-controlled study to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of multiple doses of ONO-2808 in patients with Multiple System Atrophy (MSA), hereafter referred to as the core part. This is the first study of ONO-2808 in patients with MSA. Following completion of the core part, subjects may choose to continue to a parallel group extension part with an open-label treatment period to assess the long-term safety, tolerability, pharmacodynamics, and potential efficacy of ONO-2808 in patients with MSA, hereafter referred to as the extension part.

#### Core part:

The purpose of the study is to evaluate 3 doses of ONO-2808 compared to placebo in MSA patients, including: 1) safety and tolerability, 2) pharmacokinetics, and 3) changes in clinical outcome assessments (COAs) and biomarkers considered to be related to the pharmacodynamics and potential efficacy of ONO-2808.

The study will be conducted at approximately 40 sites in the US and Japan. Approximately 80 subjects will be randomized to ensure [REDACTED]

[REDACTED] Eligible subjects will be randomized in a 1:1:1:1 ratio to one of the 3 dose levels of ONO-2808 [REDACTED] or a matching placebo control. Subjects will receive blinded study treatment orally once daily (QD) for 24 weeks and will be followed up with for 4 weeks after treatment discontinuation. At the end of treatment in the core part, subjects may continue receiving treatment in an extension part of this study. [REDACTED]

Safety assessments to be performed will include Adverse Events (AEs), physical and neurological examinations, vital signs, 12-lead electrocardiograms (ECGs), hematology (including coagulation panel), clinical chemistry (including liver and kidney function test panels), urinalysis, and Columbia Suicide Severity Rating Scale (C-SSRS<sup>4</sup>) [REDACTED]

[REDACTED] Clinical outcome assessments to be performed include the Unified Multiple System Atrophy Rating Scale (UMSARS), [REDACTED]

[REDACTED] and brain and liver magnetic resonance imaging (MRI).

### Extension Part:

The extension part of the ONO-2808-03 study is a parallel-group study to assess the safety, tolerability, PD, and potential efficacy of the long-term administration of ONO-2808 in subjects with MSA.

The purpose of this extension part is to evaluate 3 doses of ONO-2808 in MSA subjects, including: 1) safety and tolerability and 2) changes in COAs and biomarkers considered to be related to the PD and potential efficacy of ONO-2808.

Subjects who complete the core part of the ONO-2808-03 study will be eligible to rollover into this extension part. Up to 80 subjects will be enrolled. Subjects who rollover from the core part into this extension part will continue the same double-blind dose assignment from the core part for 8 weeks (rollover period), ONO-2808 [REDACTED] or a matching placebo. Following the 8 weeks of double-blind treatment, and after freezing CRFs in the core part, subjects will be unblinded individually and receive open-label treatment for an additional 48 weeks. Placebo subjects (placebo group) will be [REDACTED] of ONO-2808 at the start of open-label treatment and the other subjects (active group) will continue the dose assignment from the core part. All subjects will receive study treatment orally once daily (QD) and will be followed up for 12 weeks (follow-up period) after treatment discontinuation. [REDACTED]

Safety assessments to be performed will include AEs, physical and neurological examinations, vital signs, 12-lead ECGs, hematology (including coagulation panel), clinical chemistry (including liver and kidney function test panels), urinalysis, and C-SSRS. Clinical outcome assessments to be performed include the UMSARS, [REDACTED] and brain and liver MRI (as needed).

Standard of care treatments for MSA consistent with local medical practice will be allowed during the extension part.

## **2.2 Study Objectives and Endpoints**

The primary objective of this Phase 2 study is to assess the safety of ONO-2808 in patients with MSA. The secondary and exploratory objectives are to gain confidence in the dose and proof of concept for efficacy for the next phase of development. Study objectives and corresponding endpoints are provided in [Table 2.2-1](#).

**Table 2.2-1 Study Objectives and Endpoints**

| <b>Objectives</b>        | <b>Endpoints</b>        |
|--------------------------|-------------------------|
| <b>Primary Objective</b> | <b>Primary Endpoint</b> |

| Objectives                                                                                                           | Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To evaluate the safety and tolerability of multiple oral doses of ONO-2808 in patients with MSA                      | <p>Incidence or change from the baseline in the following assessments:</p> <ul style="list-style-type: none"> <li>• Incidence and severity of adverse events (AEs)</li> <li>• Vital signs (blood pressure, pulse rate, temperature, respiratory rate)</li> <li>• 12-lead electrocardiograms (ECGs); parameters such as, but not limited to, heart rate, RR, PR, QRS, QT, and corrected QT intervals (QTcF)</li> <li>• Clinically significant abnormal physical examination findings</li> <li>• Clinically significant laboratory abnormalities (hematology, clinical chemistry, and urinalysis), including survey of drug-induced liver abnormalities.</li> <li>• Clinically abnormal findings in Columbia Suicide Severity Rating Scale (C-SSRS)</li> </ul> |
| Secondary Objectives                                                                                                 | Secondary Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| To evaluate the pharmacokinetics (PK) of multiple oral doses of ONO-2808 in patients with MSA                        | <ul style="list-style-type: none"> <li>• Plasma concentration of ONO-2808 (core part only)</li> </ul> <div data-bbox="755 1108 1417 1192" style="background-color: black; height: 40px; width: 100%;"></div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Exploratory Objectives                                                                                               | Exploratory Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| To evaluate performance of clinical outcome assessments (COA) in patients with MSA taking multiple doses of ONO-2808 | <ul style="list-style-type: none"> <li>• Change from baseline in the following assessments:</li> <li>• Unified Multiple System Atrophy Rating Scale (UMSARS)</li> </ul> <div data-bbox="719 1440 1417 1877" style="background-color: black; height: 208px; width: 100%;"></div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Objectives                                                                                           | Endpoints                                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [REDACTED]                                                                                           | <p>[REDACTED]</p> <ul style="list-style-type: none"> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>                                                                                                                                                          |
| [REDACTED]                                                                                           | <p>[REDACTED]</p> <ul style="list-style-type: none"> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>                                                      |
| To evaluate performance of imaging biomarkers in patients with MSA taking multiple doses of ONO-2808 | <p>Imaging parameters may include, but are not limited to:</p> <ul style="list-style-type: none"> <li>• Magnetic resonance imaging (MRI)* volumetric assessments of white and gray matter*</li> <li>• Diffusion tensor imaging (DTI) for white matter abnormalities*</li> </ul> |
| [REDACTED]                                                                                           | <ul style="list-style-type: none"> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>                                                                                                                                                                            |

The exploratory/secondary endpoints to assess plasma, [REDACTED] imaging, and other potential exploratory biomarkers marked with an asterisk (\*) will be reported outside the CSR. The data and interpretations arising from addressing all the other objectives will be reported in the CSR. Only analyses to be included in the CSR will be defined in this SAP

## 2.3 Randomization and Blinding

### Randomization

#### Core Part:

This is a randomized, double-blind, parallel-group, placebo-controlled Phase 2 study. The subjects who do not consent to optional procedures will be equally randomized to one of the 4 treatment arms [REDACTED] for the assessment schedule.

[REDACTED] Randomization will be performed using an interactive voice/web response system (IVRS/IWRS) or a suitable independent randomization provider. [REDACTED]

[REDACTED] A randomization number for eligible subjects in the study will be assigned in chronological order, as provided in the randomization list.

All subjects will be centrally assigned to randomized study intervention using IVRS/IWRS.

#### Extension Part:

Subjects will transition from the core part of the ONO-2808-03 study at the week 24 visit to the extension part of the ONO-2808-03 study. All subjects who are on active doses [REDACTED] as well as placebo in the core part (administered once daily [QD]) will continue in a blinded manner for 8 weeks during the rollover period and then transition to open-label treatment for the remainder of the study (48 weeks). At the start of open-label treatment, subjects previously treated with placebo will [REDACTED]. The total treatment period for the extension part is 14 months.

#### Core and Extension Parts:

Study intervention will be dispensed at the study visits as summarized in the schedule of activities (SoA) for Protocol ONO-2808-03 (Version 5.0). Returned study intervention should not be re-dispensed to the subjects.

### Blinding

The treatment for each subject will remain blinded during the 6-month core part and the 2-month rollover period of the study, until the electronic case report forms (eCRFs) for individual subject from the core part of the study are frozen at the end of the 2-month rollover period. The treatment of each individual subject will be unblinded at Visit 14 (Week 32) at the time the subject enters the 12-month open-label treatment period by the data management team. Investigators, all staff at each trial site, and subjects will be blinded to treatment allocation until subjects enter the 12-month open-label treatment period.

[REDACTED]

In the event of a medical emergency for which the treatment assignment needs to be known to manage the treatment of a study subject before a study subject enters the 12-month open-label treatment period, unblinding information may be requested by the Investigator or qualified designee. Unblinding at the study site for any other reason will be considered as a protocol deviation.

The blind should be maintained for those involved in the data analysis of the study and those involved in the ongoing conduct of the study (i.e., the study management, monitors, and Investigator) until the conclusion of the rollover period in the extension part.

## 2.4 Duration of Subject Participation

Potential subjects will undergo a screening period of up to 6 weeks. Eligible subjects will be assigned to receive one of 3 dose levels [REDACTED] of ONO-2808 or a placebo control. ONO-2808 or placebo will be administered orally once daily (QD) for 24 weeks to subjects, who will be followed for 4 weeks after treatment discontinuation if not consenting to participate in the extension part. After the completion of treatment in the core part, subjects may continue treatment in the extension part. Completers of the core part who wish to continue treatment will rollover to the extension part at the week 24 visit. All subjects who are on active doses [REDACTED] in the core part will continue taking the same dose through the entire extension part. All placebo subjects will continue the placebo (administered QD) for 8 weeks during the rollover period and then [REDACTED] dose for the remainder of the study (48 weeks). The total treatment period for the extension part is 14 months.

Dose modifications for subjects are not allowed during the study; however, drug interruptions will be allowed based on the judgement of the Investigator in conjunction with the Sponsor. If a subject experiences AEs that meet the individual stopping criteria during treatment with ONO-2808, the subject will be discontinued from further treatment and followed for safety outcomes.

[REDACTED] Institutional Review Board/Independent Ethics Committee (IRB/IEC), or competent health authority, after consideration of all available safety data and with reference to the stopping rules as defined in the protocol [Section 7.1 Discontinuation of Study Intervention](#). If a patient experiences a non-transaminitis or non-DILI-related (non-drug-induced liver injury-related) AE that does not meet the individual stopping criteria, but would warrant a temporary pause in treatment, this can be done with Sponsor approval to allow an opportunity for AE resolution.

A dose interruption will not exceed 2 weeks, the time required to achieve pharmacokinetic steady state. Treatment delays of longer than 2 weeks will be considered on a case-by-case basis and may result in the discontinuation of the subject from active treatment.

Upon resolution of an AE (other than transaminitis or DILI), Investigational Medicinal Product (IMP) can be restarted. If reintroduction of the IMP triggers a reappearance of an AE, permanent discontinuation is required.

### **3 HYPOTHESIS TESTING AND SIGNIFICANCE LEVEL**

In this study, no statistical hypotheses are planned to be tested and all analyses are descriptive only.

#### **3.1 Multiplicity Adjustment**

Not applicable.

## **4 TIMING OF PLANNED ANALYSIS**

Database lock and the final analysis will be performed when all subjects enrolled have been evaluated and have completed the follow-up visit after the extension part. A subject is considered to have completed the study if the subject has completed all periods of the study including the last visit and the last scheduled procedure shown in the SoA of the protocol. The date of completion of the subject is defined as the date of last visit of the last scheduled procedure for the study. The date of completion or discontinuation is to be recorded in the eCRF.

An interim analysis is planned after the last subject from the core part completes V13 (Week 24) or discontinued prior to V13. For the details of the interim analysis (see section [21](#)).

## 5 SAMPLE SIZE

The planned sample size for the core study is [REDACTED] completed subjects, or [REDACTED] per treatment group, including placebo.

Sample size and statistical power were calculated for the overall treated cohort in the core part [REDACTED] to detect a transaminitis event rate as high as that seen during Phase 1 healthy volunteer studies of ONO-2808 [REDACTED]

At the level of an individual subject, the probability (p) that an individual subject will experience an event of interest follows a Bernoulli distribution. For the purposes of calculating power and sample size for the sample of interest, the binomial distribution is used. The probability (p) that a given subject has no transaminitis event during 24 weeks of treatment in the core part = 1-p. The probability of no transaminitis events out of n subjects = (1-p)<sup>n</sup>. At 95% power, we set n subjects (from above) equal to 1 - power = 1 - 0.95 = 0.05. To determine sample size for the overall treated cohort in the core part [REDACTED] we solve for:

$$(1 - [REDACTED])^n = 0.05$$

$$n \times \ln([REDACTED]) = \ln(0.05)$$

$$n = \ln(0.05) / \ln([REDACTED]) = [REDACTED] \text{ subjects (3 arms with } n = [REDACTED])$$

At the level of individual treatment arms (n = [REDACTED]) a sensitivity analysis was performed to evaluate power at various transaminitis event rates using the method outlined above (Table 5-1).

**Table 5-1 Power for selected event rates, per treatment arm**

| Event Rate | Power      |
|------------|------------|
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |

Assuming a drop-out rate of up to [REDACTED], a total of approximately 80 subjects (20 per arm) are to be randomized into the study, to ensure [REDACTED] evaluable subjects for analysis in the core part.

### 5.1 Sample Size by Region

Not applicable for this study.

### 5.2 Sample Size re-estimation

Not applicable for this study.

## **6 ANALYSIS SETS**

Enrolled subjects are all subjects who agree to participate, or through a legally acceptable representative agrees to participate, in the trial following completion of the informed consent process.

### **Safety Analysis Set**

The Safety Analysis Set for Core part (SAF-C) will be based on all subjects who have signed the Informed Consent Form (ICF) and who have received at least one dose of study treatment. Subjects in the SAF will be grouped by dose level of study treatment actually received, irrespective of the assigned dose level of study treatment. The SAF-C will be used for all safety analyses in the core part and overall.

The Safety Analysis Set for Extension part (SAF-E) will be based on all subjects who have signed the ICF at the Rollover visit (Visit 13/Week 24) and did rollover into the extension part and who have received at least one dose of study treatment in the extension part. Subjects in the SAF-E will be grouped by dose level of study treatment received, irrespective of the assigned dose level of study treatment. The SAF-E will be used for all safety analyses in the extension part.

### **Full Analysis Set**

The Full Analysis Set (FAS) will be the primary analysis set used for assessment of efficacy and will be based on all subjects who have been randomized. This may include subjects who have not been treated with ONO-2808 (i.e., following the Intention-To-Treat [ITT] principle). Subjects in the FAS will be grouped by dose level of study treatment as assigned at randomization. The FAS will be used for all efficacy analyses. FAS for the Extension part (FAS-E) will include all subjects who have been randomized and rolled over into the extension part.

### **Pharmacokinetic Analysis Set**

The Pharmacokinetic Analysis Set (PKS) will include subjects who have signed the ICF and have received at least one dose of study treatment, and from whom results of plasma concentrations have been obtained for a sufficient number of sampling time points that are suitable for analysis.

The PKS will be used for all PK analyses.

Demographic and baseline characteristics will be summarized for the SAF (SAF-C and SAF-E), FAS, and PKS populations. If any of the SAF, FAS, and PKS populations are identical, only one composite of SAF/FAS/PKS population may be used for summary purposes.

## 7 GENERAL STATISTICAL CONSIDERATIONS

### 7.1 Software to be used in Analyses

SAS® version 9.4 or higher will be used for all analyses and the production of outputs in this study.

### 7.2 Output Conventions

Unless otherwise stated, descriptive statistics including the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum will be presented for continuous variables (in the case of SD, when the number of subjects is more than or equal to two).

In general, the mean and median will be reported to one additional decimal place compared to the original data. The SD will be reported to two additional decimal places compared to the original data, and the minimum and maximum will be reported to the same number of decimal places as the original data. Also, unrounded original data will be used in calculations.

**Table 7.2-1 Derived variables and decimal places to display for original data**

| Derived variables                        | Decimal places to display for original data |
|------------------------------------------|---------------------------------------------|
| BMI (kg/m <sup>2</sup> )                 | One decimal place                           |
| Total exposure to study treatment (days) | One decimal place                           |
| QTcF (ms)                                | One decimal place                           |
| QTcB (ms)                                | One decimal place                           |
| Corrected calcium (mmol/L)               | One decimal place                           |
| Corrected calcium (mg/dL)                | One decimal place                           |
| Creatinine clearance                     | One decimal place                           |

Frequencies and percentages will be presented for categorical variables. Unless otherwise stated, percentages for scheduled assessments will be based on the number of non-missing values. Otherwise, percentages (for example, for Adverse Events and Concomitant Medications) will be calculated based on the total number of subjects in the analysis set. If the analysis set is not stated in the title, then a footnote will clarify the denominator used. Percentages will be reported to one decimal place throughout, unless the percentage is 100 (in which case no decimal places will be presented) or unless the frequency count is zero (in which case no percentage will be presented).

A month is counted as 30.4375 days, and a year is counted as 365.25 days (30.4375 days × 12 months).

For medical history and Adverse Events, frequency ordering will be used for the summary table presentation (i.e. by alphabetical order for each System Organ Class (SOC), followed by descending frequency of Preferred Term (PT) within each SOC by the overall group; in the case of equal PT frequency, alphabetical order will be applied).

All data will be listed as recorded on the eCRF, sorted by dose level/study treatment, site identifier, subject identifier, and visit (where applicable) and date (and time) of event/assessment (where applicable).

### 7.3 General Data Handling Conventions

In general, missing data values will be recorded as missing and will not be imputed for the statistical analysis, unless specified otherwise. Only recorded data values will be used for the reporting of descriptive statistics, unless specified otherwise.

#### Missing Dates/Times:

In cases of missing or incomplete dates (e.g., Adverse Events and concomitant medications), the missing component(s) will be imputed for analysis purposes, assuming the most conservative value possible. For imputation algorithms for Concomitant Medications, see section 14.1, and for imputation algorithms for Adverse Events, see Section 17.2.1. Observed data values as they appear in the eCRF will be presented in the data listings.

#### Inequalities:

Safety assessment values of the form of “< x” (i.e., below the lower limit of quantification) or “> x” (i.e., above the upper limit of quantification) will be imputed as “x” in the calculation of descriptive statistics but displayed as “< x” or “> x” in any listings that are produced.

### 7.4 Re-screened Subjects

In the case of retests for screening data, re-screened subjects will be issued a new Subject identifier (ID) number. Each subject will have one unique Subject ID with different Subject ID numbers for each screen attempt. A record will be kept in the eCRF of all re-screened subjects’ original Subject ID number, which will be provided in a subject disposition listing. For a re-screened subject, the latest measurements will be used for the outputs.

### 7.5 Baseline definition

Baseline measurements will be defined as the last non-missing observation on or before the date (e.g., regardless of time) of the first administration of ONO-2808 or placebo control, considering both scheduled and unscheduled visits in each study part (core and extension). If two values are equally eligible (the order cannot be determined by the data (e.g., same date without time) to assess subject status at baseline, then the mean of the relevant assessments can be taken as the baseline value. For triplicate 12-lead ECG measurements performed at the same scheduled time points, the mean of the 3 values should be used. Non-missing measurements obtained at Visit 13 (Week 24) or non-missing measurements obtained at scheduled or unscheduled visits before administering of ONO-2808 or placebo control in the extension part will be used as baseline measurements for the extension part.

The change from baseline for a parameter is calculated as: (observed value at visit – baseline value), in each study part and overall.

For subjects with observations in two separate periods or positions (such as fed and fasted periods or standing and supine), the period-specific or position-specific baseline will be used for analyses if collected.

### 7.6 Study Day

Study day 1 is the day of the first administration of ONO-2808 or placebo. Each study assessment date (i.e., start or stop date, etc.) will be assigned a study day calculated as follows:

- If the date < date of study day 1, then study day = (date – date of study day 1)
- If the date >= date of study day 1, then study day = ((date – date of study day 1) +1)

## 7.7 Handling Rules for Time Points

For any presentations which summarize values by visit, time windows will be defined. Inclusion within the time window should be based upon the actual date of the visit rather than the intended date so that all unscheduled visit data (including unscheduled early termination visits) have the potential to be included in the summaries. The window for the visits is dependent upon the visit schedule for the data type but will follow the same principle in terms of construction so that the upper limit of the interval falls halfway between the two visits (note that if there are an even number of days between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day). Note that for 12-lead ECG, when multiple triplicate sets qualify for the same analysis window, the date and/or time of the last of the triplicate assessments will be used for the time windowing for the entire triplicate set.

For summaries, the closest value (or the latter in the situation where values are equidistant from the date) to the scheduled visit will be used. All values (scheduled or unscheduled) will be presented in a listing, with those values contributing to the visit-based summary clearly identified.

When deriving subject level statistic (e.g., maximum value post baseline), all values should be included regardless of whether they appear in a corresponding visit-based summary, including unscheduled values.

In the case of a retest, the later value will be used for summary and analysis purposes. In the case of test results with identical timepoints, the average of the measurements will be taken.

For the visit day, data will be analyzed using nominal study visits as defined in the study schedule in the protocol. For example, the time windows for vital signs data (collected weekly) in the core and the extension parts are presented in [Table 7.7-1](#) and [Table 7.7-2](#), respectively.

The time windows for 12-ECG in the core and extension parts are presented in [Table 7.7-3](#) and [Table 7.7-4](#), respectively.

The time windows for subject reported outcome assessments listed in Section 20 (i.e., UMSARS, [REDACTED] etc.) data (collected on site visit) in the core and the extension parts are presented in [Table 7.7-5](#) and [Table 7.7-6](#), respectively.

The time windows for plasma pharmacokinetic sampling in the core part are presented in [Table 7.7-7](#).

**Table 7.7-1 Time Windows for Vital Signs (Core Part)**

| Nominal Visit (Scheduled Visit) | Scheduled Visit Day (Study Day) | Time windows  |
|---------------------------------|---------------------------------|---------------|
| Baseline                        | 1                               | - 3 to 1 day  |
| Week 1                          | 8                               | 2 to 11 days  |
| Week 2                          | 15                              | 12 to 18 days |
| Week 3                          | 22                              | 19 to 25 days |
| Week 4                          | 29                              | 26 to 32 days |

| <b>Nominal Visit (Scheduled Visit)</b> | <b>Scheduled Visit Day (Study Day)</b> | <b>Time windows</b> |
|----------------------------------------|----------------------------------------|---------------------|
| Week 5                                 | 36                                     | 33 to 39 days       |
| Week 6                                 | 43                                     | 40 to 50 days       |
| Week 8                                 | 57                                     | 51 to 64 days       |
| Week 10                                | 71                                     | 65 to 78 days       |
| Week 12                                | 85                                     | 79 to 99 days       |
| Week 16                                | 113                                    | 100 to 127 days     |
| Week 20                                | 141                                    | 128 to 155 days     |
| Week 24                                | 169                                    | 156 to 183 days     |

\*For completers from the core part who do not wish to continue to the extension part

**Table 7.7-2 Time Windows for Vital Signs (Extension Part)**

| <b>Nominal Visit (Scheduled Visit)</b> | <b>Scheduled Visit Day (Study Day)</b> | <b>Time windows</b> |
|----------------------------------------|----------------------------------------|---------------------|
| Week 24 (Baseline)                     | 169                                    | 156 to 197 days     |
| Week 32 (Open label)                   | 225                                    | 198 to 228 days     |
| Week 33                                | 232                                    | 229 to 235 days     |
| Week 34                                | 239                                    | 236 to 242 days     |
| Week 35                                | 246                                    | 243 to 249 days     |
| Week 36                                | 253                                    | 250 to 256 days     |
| Week 37                                | 260                                    | 257 to 263 days     |
| Week 38                                | 267                                    | 264 to 274 days     |
| Week 40                                | 281                                    | 275 to 288 days     |
| Week 42                                | 295                                    | 289 to 302 days     |
| Week 44                                | 309                                    | 303 to 323 days     |
| Week 48                                | 337                                    | 324 to 351 days     |
| Week 52                                | 365                                    | 352 to 379 days     |
| Week 56                                | 393                                    | 380 to 435 days     |
| Week 68                                | 477                                    | 436 to 519 days     |
| Week 80                                | 561                                    | 520 to 575 days     |
| Week 84                                | 589                                    | 576 to 617 days     |
| Week 92                                | 645                                    | 618 to 672 days     |

**Table 7.7-3 Time windows for 12-ECG (Core part)**

| <b>Nominal Visit (Scheduled Visit)</b> | <b>Scheduled Visit Day (Study Day)</b> | <b>Time windows</b> |
|----------------------------------------|----------------------------------------|---------------------|
| Baseline                               | 1                                      | - 3 to 1 day        |
| Week 1                                 | 8                                      | 2 to 11 days        |
| Week 2                                 | 15                                     | 12 to 22 days       |
| Week 4                                 | 29                                     | 23 to 43 days       |
| Week 8                                 | 57                                     | 44 to 71 days       |
| Week 12                                | 85                                     | 72 to 99 days       |
| Week 16                                | 113                                    | 100 to 127 days     |
| Week 20                                | 141                                    | 128 to 155 days     |
| Week 24                                | 169                                    | 156 to 183 days     |
| Week 28*                               | 197                                    | 184 to 211 days     |

\*For completers from the core part who do not wish to continue to the extension part

**Table 7.7-4 Time windows for 12-ECG (Extension part)**

| <b>Nominal Visit (Scheduled Visit)</b> | <b>Scheduled Visit Day (Study Day)</b> | <b>Time windows</b> |
|----------------------------------------|----------------------------------------|---------------------|
| Week 24 (Baseline)                     | 169                                    | 156 to 197 days     |
| Week 32 (Open label)                   | 225                                    | 198 to 228 days     |
| Week 33                                | 232                                    | 229 to 235 days     |
| Week 34                                | 239                                    | 236 to 246 days     |
| Week 36                                | 253                                    | 247 to 260 days     |
| Week 38                                | 267                                    | 261 to 274 days     |
| Week 40                                | 281                                    | 275 to 295 days     |
| Week 44                                | 309                                    | 296 to 323 days     |
| Week 48                                | 337                                    | 324 to 351 days     |
| Week 52                                | 365                                    | 352 to 379 days     |
| Week 56                                | 393                                    | 380 to 435 days     |
| Week 68                                | 477                                    | 436 to 519 days     |
| Week 80                                | 561                                    | 520 to 575 days     |
| Week 84                                | 589                                    | 576 to 617 days     |
| Week 92                                | 645                                    | 618 to 672 days     |

**Table 7.7-5 Time windows for subject reported outcome assessments (Core part)**

| Nominal Visit (Scheduled Visit) | Scheduled Visit Day (Study Day) | Time windows    |
|---------------------------------|---------------------------------|-----------------|
| Baseline                        | 1                               | - 3 to 1 day    |
| Week 12                         | 85                              | 2 to 127 days   |
| Week 24                         | 169                             | 128 to 196 days |

**Table 7.7-6 Time windows for subject reported outcome assessments (Extension part)**

| Nominal Visit (Scheduled Visit) | Scheduled Visit Day (Study Day) | Time windows    |
|---------------------------------|---------------------------------|-----------------|
| Week 24 (Baseline)              | 169                             | 156 to 197 days |
| Week 32 (Open label)            | 225                             | 198 to 253 days |
| Week 40                         | 281                             | 254 to 309 days |
| Week 48                         | 337                             | 310 to 365 days |
| Week 56                         | 393                             | 366 to 435 days |
| Week 68                         | 477                             | 436 to 519 days |
| Week 80                         | 561                             | 520 to 575 days |

**Table 7.7-7 Time windows for Plasma Pharmacokinetics sampling (Core part)**

| Nominal (Scheduled) Visit/Day | Hours after Dose | Time windows  |
|-------------------------------|------------------|---------------|
| Week 2/Day 14                 | Pre-dose         | <0 hours      |
| Week 8/Day 56                 | Pre-dose         | <0 hours      |
| Week 12/Day 85                | Pre-dose         | <0 hours      |
|                               | 3 hours          | 0 - ≤ 4 hours |
|                               | 5 hours          | 4 - ≤ 6 hours |
| Week 24/Day 169               | Pre-dose         | <0 hours      |
|                               | 3 hours          | 0 - ≤ 4 hours |
|                               | 5 hours          | 4 - ≤ 6 hours |

## 7.8 Multi-center Studies

As the number of subjects at each center is expected to be small, center effects will not be considered in the analysis of data for this study.

## 7.9 Definition of covariates and subgroup factors

The classification for the stratification factors used for the randomization will be based on the values entered the randomization system; all other covariates will be based on values recorded on the eCRF and categorizations for these will be defined as necessary. Note that if overly sparse data results from these categorizations, then, if there is scope to do so, it is permitted to combine

appropriate category groups to provide a sufficient number of observations to enable meaningful interpretation of the analysis results.

Other baseline variables may also be assessed if there is clinical justification, or an imbalance is observed between the study treatments.

### 7.9.1 Covariates

The covariates detailed below will be investigated for the primary and secondary outcome variables, in addition to the stratification factors (as indicated in section 2.3). This is for exploratory purposes to ascertain whether any covariate is found to modify the study intervention effect.

**Table 7.9-1 Covariates**

| Factors     | Categories                                                                                                                |
|-------------|---------------------------------------------------------------------------------------------------------------------------|
| Age (years) | <65, >= 65                                                                                                                |
| Sex         | Male, Female                                                                                                              |
| Race        | White, Black/African American, Asian, Other [Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native] |
| Region      | USA, Japan                                                                                                                |
|             |                                                                                                                           |

Additional categories to be analyzed for some factors may be determined prior to database lock.

### 7.9.2 Subgroup Factors

The purpose of subgroup analyses is to assess the consistency of study treatment effect across expected prognostic/predictive factors.

Table 7.9-1 in section 7.9.1 provides the subgroups (values are at baseline, unless otherwise stated) to be analyzed.

No adjustment will be made for covariates. However, if emerging data shows that certain baseline factors may be prognostic/predictive, then these may be investigated as an exploratory analysis.

## 8 SUMMARY OF STUDY ENDPOINTS AND ANALYSIS SETS

**Table 8-1 Summary of Outcome Variables and Analysis Sets**

| Outcome Variable                          | Analysis Sets | SAP Section          |
|-------------------------------------------|---------------|----------------------|
| <u>Safety</u>                             |               |                      |
| -Adverse Events and deaths                | SAF           | <a href="#">17.2</a> |
| -Clinical laboratory evaluations          | SAF           | <a href="#">17.3</a> |
| -Physical examinations                    | SAF           | <a href="#">17.4</a> |
| -Vital signs                              | SAF           | <a href="#">17.5</a> |
| -12-Lead ECGs                             | SAF           | <a href="#">17.6</a> |
| -C-SSRS                                   | SAF           | <a href="#">17.7</a> |
| <u>Study Population/Demography</u>        |               |                      |
| -Demographic and Baseline characteristics | SAF, FAS, PKS | <a href="#">11</a>   |
| -Medical history                          | SAF           | <a href="#">12</a>   |
| -Disease Specific Characteristics         | SAF, FAS, PKS | <a href="#">13</a>   |
| -Prior and Concomitant medications        | SAF           | <a href="#">14</a>   |
| -Exposure/Compliance and Tolerability     | SAF, FAS      | <a href="#">15</a>   |

## 9 SUBJECT DISPOSITION

Subject disposition will be summarized for all Enrolled subjects in terms of counts and percentages. The following subject disposition categories will be summarized by study treatment groups, and overall, in each part of the study:

### Core part:

- Subjects who signed informed consent
- Subjects who were screen failures  
Screen failures are defined as the subjects who were discontinued from the screening period.
- Subjects who were eligible for randomization  
Subjects who were eligible for randomization are defined as the subjects who satisfied all eligibility criteria.
- Subjects who were randomized
- Subjects who were randomized but not treated
- Subjects who were treated (i.e., subjects who have received at least one dose of study treatment)
- Subjects who completed the treatment period of the core part of the study
- Subjects who completed the core part of the study (Double-blind study treatment period and safety follow-up)
- Subjects who completed the treatment period but discontinued during the safety follow-up of the core part of the study
- Subjects who discontinued during the treatment period of the core part of the study
- Subjects who discontinued during the treatment period and discontinued from the safety follow-up of the core part of the study
- Subjects who discontinued during the treatment period and completed the safety follow-up of the core part of the study
- Subjects who completed the core part of the study and opted to continue into the extension part of the study
- Subjects receiving intended doses/total exposure (in weeks) during the core part of the study using the following categories: 0 - <4 weeks, 4 - <8 weeks, 8 - <12 weeks, 12 - <16 weeks, 16 - <20 weeks, and 20 - <24 weeks.

The denominators for subjects who were screen failures and subjects who were eligible for randomization are all Enrolled subjects, and the other denominators are the number of randomized subjects.

Extension part:

- Subjects who signed informed consent
- Subjects who were eligible for the extension part of the study
- Subjects who entered the extension part of the study
- Subjects who entered the extension part of the study but not treated
- Subjects who continued to receive treatment
- Subjects who completed the treatment period of the extension part of the study
- Subjects who completed the extension part of the study (study treatment period and safety follow-up)
- Subjects who completed the treatment period but discontinued during the safety follow-up of the extension part of the study
- Subjects who discontinued during the treatment period of the extension part of the study
- Subjects who discontinued during the treatment period and discontinued also from the safety follow-up of the extension part of the study
- Subjects who discontinued during the treatment period and completed the safety follow-up of the extension part of the study
- Subjects receiving intended doses/total exposure (in weeks) during the extension part of the study using the following categories: 24 - <32 weeks, 32 - <40 weeks, 40 - <48 weeks, 48 - <56 weeks, 56 - <64 weeks, 64 - <72 - <80 weeks, and >80 weeks.

The denominators for subjects who were eligible for the extension part and who entered the extension part but were not treated are all subjects who were eligible for the extension part, and the other denominators are number of subjects who received treatment in the extension part of the study.

Core part and Extension part:

For subjects who were screen failures, those withdrawn from the study treatment period, and those withdrawn from the study (including lost to follow-up), the reason(s) will be summarized in the same output.

The number and percentage of subjects in each defined analysis set will also be tabulated for each study treatment group and overall, in each study part and overall.

All subject disposition data will be listed for all Enrolled subjects.

## 10 PROTOCOL DEVIATIONS

Important protocol deviations (IPDs) are defined as a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Protocol deviations will be captured for evaluation using the following methods:

- Programmed protocol deviation checks
- Medical review (e.g., prohibited medications)
- Review of a non-compliance/protocol deviation tracker

Protocol deviations will be reviewed on an ongoing basis and the final review and classification of protocol deviations will be performed prior to database lock.

The following general categories will be considered IPDs:

- Inadequate informed consent/re-consent.
- Inappropriate review by Institutional Review Board (IRB).
- Unreported or late reported SAEs.
- Deviation from inclusion and exclusion criteria
- Improper handling/storage of investigational medicinal products (IMPs).
- Incorrect study treatment assignment or randomization error.
- Incorrect dosage and administration of IMPs.
- Use of prohibited concomitant medication and therapy
- A study participant meets protocol defined withdrawal criteria during the study but is not withdrawn by the investigator
- Other (PDs that do not fit into any of the above categories but are considered to be an important PD)

Note: The following important PDs will be categorized as the PD category “Other”:

- Missed safety or efficacy assessments related to primary or secondary endpoints.
- Safety or efficacy endpoint (primary/secondary) data collected using inadequate or improperly calibrated equipment, not fulfilling protocol requirements.
- The “Other” category varies by study and is determined by critical data or critical process in the study.
- Important PD that is not addressed in any of the above categories

Deviations that may not be considered an IPD include sites not reporting a SAE within 24 hours of knowledge of the event, subjects not consenting to optional procedures, small deviations from protocol-specified visit windows, a protocol required assessment not completed or not completed correctly, subject who missed dosing for a reason other than specified in the protocol, a failure to

perform study procedure not relevant for safety monitoring, and eligible subjects not receiving study treatment.

The number and percentage of subjects with “IPDs” (with details of category of deviation) will be summarized by study treatment groups and overall, in each study part (core and extension) and overall.

In addition, all protocol deviations related to COVID-19 will be listed separately.

The need for any supplementary analyses resulting from protocol deviations will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

All protocol deviations will be listed for all Enrolled subjects.

## 11 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subjects' demographic and baseline characteristics will be summarized for all subjects in the SAF (SAF-C and SAF-E), FAS, and PKS.

The following demographic and baseline characteristics will be summarized using frequencies and percentages.

- Sex (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Medical history (Yes, No)

The following demographic and baseline characteristics will be summarized using frequencies and percentages based on the following categories:

- Age (<30, 30- <50, 50- <65, 65- <75,  $\geq 75$ )
- Body Mass Index (BMI) (<18.5, 18.5- <25, 25- <30,  $\geq 30$ )

The following demographic and baseline characteristics will be summarized with descriptive statistics.

- Age (years)
- Height (cm)
- Body weight (kg)
- BMI ( $\text{kg}/\text{m}^2$ )
  - $\text{BMI (kg/m}^2\text{)} = \text{Body weight (kg)} / \{\text{Height (m)}\}^2$

Summary statistics will be presented by the study treatment group and overall, in each study part (core and extension) and overall.

For the extension part, Height and Age at Week 0 and Body weight and BMI at Week 24 (Visit 13) will be used as baseline.

All subject demographic and baseline characteristics will be listed for all Enrolled subjects.

## **12 MEDICAL HISTORY**

All analysis of medical history information will be based on all subjects in the SAF.

The reported medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>). Medical history results will be summarized by SOC and Preferred Term (PT) for each study treatment group and overall for the core part only.

All medical and surgical history information will be listed for all Enrolled subjects.

Subjects' baseline primary disease characteristics will be summarized for all subjects in SAF, FAS, and PKS.

Baseline UMSARS total score, UMSARS-1 score (total score for historical review, 12 items), UMSARS-2 (total score for motor examination, 14 items), UMSARS-3 score (total score for historical review without item 11 (sexual function), 11 items), and modified UMSARS score will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

- Primary disease
  - Subtype of MSA (Likely MSA Parkinsonian subtype [MSA-P], Likely MSA cerebellar subtype [MSA-C])
  - Symptoms associated with MSA
    - Parkinsonism (Yes, No)
    - Ataxia (Yes, No)
    - Orthostatic hypotension (Yes, No)
    - Urinary dysfunction (Yes, No)
    - Other (Yes, No)

\_\_\_\_\_

\_\_\_\_\_

- Page 39 of 74

## 14 PRIOR AND CONCOMITANT MEDICATIONS

### 14.1 Analysis Items and Data Handling

Medications used by subjects in this study will be coded using the World Health Organization Drug Reference List (WHO-DRL WHODrug-Global-B3-202503), which employs the Anatomical Therapeutic Chemical (ATC) classification system. ATC level 4 and Preferred Name will be reported.

Prior medications include medications that were taken and stopped prior to the first dose of study treatment.

Concomitant medications are medications that were taken on or after the first dose of study treatment (including those for which the medication course commenced prior to the first dose of study treatment and continued after the first dose of treatment). Any medications used to treat AEs during the study will be recorded as concomitant medications.

Table 14.1-1 shows the algorithm for assigning Prior/Concomitant Medication status. For the purposes of the below algorithm, note that if start or end dates are partial or missing, then use the missing date imputation rules found in APPENDIX 1). All observed and imputed dates will be listed.

**Table 14.1-1 Algorithm for Assigning Prior and Concomitant Medication Status**

| Condition                                                                                                                                                                        | Action                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| If start and end dates are both known                                                                                                                                            | If end date < study treatment start date, assign as Prior                                                                                                                                                     |
|                                                                                                                                                                                  | - If end date $\geq$ study treatment start date and start date $\leq$ study treatment end date + 28 days*, assign as Concomitant for subjects who opted to not continue into the extension part of the study. |
|                                                                                                                                                                                  | - If end date $\geq$ study treatment start date and start date $\leq$ study treatment end date, assign as Concomitant for subjects who opted to continue into the extension part of the study.                |
| If the start and/or end dates are partial or missing (but not both missing), use the imputation rules from Appendix I, followed by the algorithm from above as if both are known |                                                                                                                                                                                                               |
| If both start and end dates are completely missing, assign as Concomitant.                                                                                                       |                                                                                                                                                                                                               |

\* 28 days signifies the safety follow-up

### 14.2 Analysis Methods

Prior and concomitant medications will be summarized by study treatment group and overall in each study part (core and extension) and overall by ATC level 4 and Preferred Name for the SAF.

Where a subject may have taken two or more of the same medication, the subject will be counted only once within a Preferred Name. Also, the same subject may contribute to two or more Preferred Names in the same classification but will only be counted once within the classification. Frequency

ordering will be used for the table presentation (i.e. by alphabetical order for ATC, followed by descending frequency for each Preferred Name within ATC for the overall group; in the case of equal Preferred Name frequencies, items would be ordered alphabetically). All prior and concomitant medications will be presented in a listing for all Enrolled subjects. A flag will be added to indicate whether a medication is prior or concomitant.

## 15 STUDY MEDICATION EXPOSURE/COMPLIANCE AND TOLERABILITY

The extent of exposure to ONO-2808 will be summarized using the SAF and FAS, by study treatment group and overall. Frequency and percentage of subjects receiving intended doses [REDACTED] by study treatment group in each study part (core and extension) and overall will be provided. In addition, the frequency and percentage of subjects experiencing dose delays will be tabulated.

The extent of exposure to ONO-2808 will be summarized using the exposure form (e-diary). In addition, the extent to exposure to ONO-2808 will also be summarized using the mixed exposure form and drug compliance log form. Drug compliance form was added for only USA sites since many subjects from the US sites did not have good compliance entering the daily oral dosing into the e-diary.

For the core part of the study, “drug compliance log” form was added at V13 (Week 24, End of Core part) and at Early Termination (ET) visit for the subjects from the USA sites only. This form was completed retrospectively using the drug accountability form and/or other sources by the sites. The drug compliance log form includes total pills taken, total pills returned, and total missed pills during the core part period (i.e., from randomization date until the end of core part or early termination).

For the extension part of the study, the drug compliance log form was added [REDACTED] (V14, V21, V24, V26, V27, and V28) and ET visits for the subjects from the USA sites only. Total pills taken, total pills returned, and total missed pills were collected from [REDACTED] (i.e., from V14 to V21, from V21 to V24, etc.).

### 15.1 Analysis Items and Data Handling

#### Total exposure to ONO-2808 (weeks):

Total exposure to ONO-2808 (weeks) = (date of last dose of ONO-2808 – date of first administration of ONO-2808) + 1)/7.

Date of first dose administration of ONO-2808 and date of last dose of ONO-2808 will be obtained from the exposure form.

If the date of first dose entry in the e-diary is missing, the date of first administration of ONO-2808 will be imputed as Randomization date for the core part and as date of V13+1 for the extension part.

For the subjects from USA sites, when drug compliance log form is used to calculate the total exposure to ONO-2808, the date of first administration of ONO-2808 is Randomization date for the core part and the date of V13+1 for the extension part and the date of last dose of ONO-2808 will be the date of the end of treatment period (V13) or date of the ET visits for the core part and the date of last dose of ONO-2808 will be the date of the end of treatment period of extension part or the date of ET visits during the extension period for the extension part.

For subjects still on treatment with ONO-2808 at the time of cut-off, the data cut-off date will be used as the last dose date to compute the total exposure.

Actual exposure to ONO-2808 (weeks):

For the subjects from the Japan sites, the actual exposure to ONO-2808 (weeks) will be calculated using the exposure form based on the following formula:

Actual exposure to ONO-2808 (weeks) = (Total exposure to ONO-2808 (days) – number of days not dosed)/7.

Number of days not dosed includes days with no dose taken per patient in the e-diary.

For the subjects from USA sites, the actual exposure to ONO-2808 (weeks) will be calculated using the drug compliance log form, which will use drug accountability form, based on the following formula:

Actual exposure to ONO-2808 (weeks) = (Total pills taken/2)/7

Actual total dose of ONO-2808 [REDACTED]

The actual total dose of ONO-2808 [REDACTED] is the actual cumulative dose of ONO-2808 delivered up to the actual last day of dosing [REDACTED] for each subject.

Relative Dose Intensity (RDI) (%):

RDI is the percentage of actual dose delivered relative to the intended dose through treatment discontinuation. RDI will be calculated as follows:

$RDI = 100\% \times d/D$

where d is the actual cumulative dose delivered up to the actual last day of dosing (i.e. the actual total dose defined above) and D is the intended cumulative dose up to the last day of dosing [REDACTED] D is the total planned dose that would be delivered.

RDI will be tabulated for subjects falling into the following categories: <50%, ≥50% - <70%, ≥70% - <90%, ≥90% - ≤100%, and >100%.

## **15.2 Analysis Methods**

Summary statistics (n, mean, median, SD, maximum, and minimum) will be presented for the total exposure to ONO-2808 (weeks), actual exposure to ONO-2808 (weeks), actual total dose of ONO-2808 [REDACTED], and RDI (%) by the study treatment group in each study part (core and extension) and overall. The number and percentage of subjects in each of the above percent RDI categories will be provided by the study treatment group in each study part (core and extension) and overall. All exposure data and study drug administration data will be listed by the study treatment group and overall for all Enrolled subjects. For subjects with total planned dose not administered, the reasons will be listed.

## **16 EFFICACY**

Not applicable.

## **17 SAFETY**

Safety analyses will be primarily descriptive and will be based on the SAF (SAF-C and SAF-E).

Summaries will be presented by the study treatment group and overall in each study part (core and extension) and overall. Unless otherwise stated, all safety analyses will be performed using data obtained between the date of first administration of ONO-2808 up to 28 days after last administration of ONO-2808.

### **17.1 Dose Limiting Toxicities**

Not applicable for this study.

### **17.2 Adverse Events and Deaths**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered to a pharmaceutical product and which does not necessarily have a causal relationship with ONO-2808. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, regardless of whether the event is causally related to the investigational product. Treatment-emergent adverse events (TEAEs) are defined as any AE with a start date on or after the ONO-2808 start date and no later than 28 days after last administration of ONO-2808. This includes: i) any AE that emerges during ONO-2808 (having been absent before ONO-2808 start) or ii) any AE that worsens after start of ONO-2808 (having been present before ONO-2808 start but at a lower intensity/severity).

Consequently, any AE with a start date on or after the first administration of ONO-2808 and no later than 28 days after the last administration of ONO-2808 will be defined as a TEAE and used for reporting purposes. Non-TEAEs will not be summarized but will be reported in a listing unless stated otherwise.

#### **17.2.1 Analysis Items and Data Handling**

AEs will be coded by using MedDRA® Version 28.0, and classified by SOC and PT. All TEAEs will be assigned to a study treatment group based on actual treatment received.

AEs will be classified by the Investigator as “not related” or “related” when considering their relationship to study treatment and reported accordingly. TEAEs with a missing causality will be assumed (if the causality is still missing after data querying) to be missing in any applicable table summaries. Pre-treatment AEs will always be classified as “not related” to study treatment.

AEs will be classified as “mild”, “moderate”, or “severe” when considering their severity. based on the Investigator’s and/or qualified designee’s decision.

For summaries by SOC and PT, when summarizing the number of subjects, a subject with multiple events will only be counted once within each SOC, PT, and study treatment group. Furthermore, SOC and PT will be sorted by frequency (i.e., by alphabetical order for each SOC, followed by descending frequency for each PT within each SOC for the overall group; in the case of equal PT frequencies, alphabetical order will be applied). For summaries by severity, the maximum severity for each subject will be used. For summaries by category and PT, the same rules will be applied replacing SOC with category.

For the summary for TEAEs leading to death, fatal AEs will be summarized by both SOC and PT.

When it is necessary to calculate percentages, the denominator will be the total number of subjects in the SAF, unless otherwise stated, and the numerator will be the total number of subjects reporting a TEAE within the relevant category.

Where the start date of an AE is partial or missing and the end date is on or after the day of first dose of study treatment, or both the start and end dates are missing, then a “worst-case” scenario will be assumed, thus the AE is assumed to have occurred when the subject was on study treatment (i.e., treatment-emergent) unless a partial start or end date indicates otherwise. When partial AE dates are present in the data, both a partial start date and/or a partial end date will be evaluated (by imputation) to determine whether it can be conclusively established that the AE started prior to the start of study treatment or ended prior to the start of study treatment. If it cannot be conclusively established that the AE started prior to the start of study treatment or ended prior to the start of study treatment based on the partial start and/or end dates, then the AE will be considered as treatment emergent.

For preparing the summary of TEAEs by onset time subgroups, a subject with multiple events will be counted according to the earliest occurrence time and treatment assignment within each period, within the same subject. Subjects with AEs during each period will be included in the analysis. The observation period for AEs (period of treatment emergence) will be from the date of first administration of study treatment to the date of periods 1 through 3 as described below, whichever comes first.

- 1) 28 days after the last dose of study treatment
- 2) The date of death
- 3) The data cut-off date

Therefore, the denominators of each period are the number of subjects whose observation period for AEs reaches the period where the time period is defined as minimum of (28 days after the last dose of the study treatment, the date of death, the date of data cutoff) – date of first administration of study treatment + 1. PTs summarized by onset time subgroups will be presented in descending order of frequency for the overall group (i.e. order by descending frequency for each PT; in each case where there are equal frequencies items will be ordered alphabetically).

The time to onset of an AE will be calculated using the following equation:

Time to onset of AE (weeks) = [(Date of occurrence of the first AE – Date of first the administration of study treatment) + 1]/7.

- Categories for onset subgroups:

Core part: 0-4 weeks, 5-8 weeks, 9-12 weeks, 13-16 weeks, 17-20 weeks, 21-24 weeks, and >24 weeks

Extension part: 24-32 weeks, 33-40 weeks, 41-48 weeks, 49-56 weeks, 57-64 weeks, 65-72 weeks, 73-80 weeks, and >80 weeks

Table 17.2-1 shows the algorithm for determining whether a given AE is considered treatment-emergent or not. For the purposes of the below algorithm, note that if the start or end dates are partial or missing, then use the missing date imputation rules found in APPENDIX 1). All observed and imputed dates will be listed.

**Table 17.2-1 Algorithm for Assigning Treatment-emergent Adverse Event Status**

| Condition                                                                                                                                                                           | Action                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| If start and end dates are both known                                                                                                                                               | If start date < study treatment start date, or start date > study treatment end date + 28 days*, then not TEAE        |
|                                                                                                                                                                                     | if start date $\geq$ study treatment start date and start date $\leq$ study treatment end date + 28 days*, then TEAE. |
| If either the start or end dates are partial or missing (but not both missing), use the imputation rules from Appendix I, followed by the algorithm from above as if both are known |                                                                                                                       |
| If both start and stop dates are completely missing, assume TEAE                                                                                                                    |                                                                                                                       |

\* 28 days signifies the safety follow-up.

TEAEs will be assigned to the study part (Core and extension) using the following algorithms:

- For subjects who opted to not continue into the extension part of the study:
  - If start date  $\geq$  study treatment start date and start date  $\leq$  study treatment end date + 28 days, the TEAE will be evaluated in the Core part of the study.
- For subjects who continue into the extension part of the study:
  - If start date  $\geq$  study treatment start date in the Core part and start date  $\leq$  end of treatment visit of the Core part (V13), then TEAE will be assigned to the Core part.
  - If start date = end of treatment visit of the Core part (V13 or start date of Extension part), then TEAE will be assigned to both Core part and Extension part.
  - If start date  $\geq$  start date of the study treatment of the Extension part and start date  $\leq$  study treatment end date in the Extension part + 28 days (safety follow-up), then TEAE will be assigned to the Extension part.
  - If start date  $\geq$  study treatment start date and it is ongoing during the Extension part, then TEAE will be assigned only to Core part.

### 17.2.2 Analysis Methods

A data listing of all AEs, including pre-treatment AEs (as defined in section 17.2.1), will be provided, including the SOC, PT, start date, end date, Investigator's assessment of severity grade and relationship to study treatment. TEAEs will be flagged in this listing. In addition, a separate listing of all serious AEs will be provided, as well as of AEs leading to discontinuation of study treatment and of AEs leading to death.

If any subjects die during the study, relevant information (Primary Cause of Death: AE, Other, or Unknown) will be supplied in a data listing.

The AE summaries, unless stated otherwise, will be based on TEAEs. Therefore, all pre-treatment AEs will be excluded from the summary tables, unless stated otherwise. However, pre-treatment AEs that worsen/increase in severity after the first dose will be recorded as new AEs and

consequently will be regarded as treatment-emergent and thus will be included in the summary tables.

The number and percentage of subjects reporting each TEAE will be summarized by study treatment group and overall, and by both SOC and PT, in each study part (core and extension) and overall.

### **Overall Summary of Adverse Events**

An overall summary of AEs will include the following:

- Number and percentage of subjects with AEs
- Number and percentage of subjects with TEAEs\*
- Number and percentage of subjects with study treatment-related TEAEs\*
- Number and percentage of subjects with TEAEs leading to interruption of study treatment\*
- Number and percentage of subjects with study treatment-related TEAEs leading to interruption of study treatment\*
- Number and percentage of subjects with TEAEs leading to withdrawal of ONO-2808\*

Drug withdrawn: ONO-2808 should be terminated in the opinion of the Principal Investigator or sub-Investigator

- Number and percentage of subjects with study treatment-related TEAEs leading to discontinuation/withdrawal of study treatment\*
- Number and percentage of subjects with TEAEs by Outcome

If a subject has more than one outcome, the subject can appear in more than one Outcome category

- Number and percentage of subjects with study treatment-related TEAEs by Outcome
- Number and percentage of subjects with TEAEs by highest severity\*
- Number and percentage of subjects with severe study treatment-related TEAEs
- Number and percentage of subjects with TEAEs by highest relationship to study treatment\*

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Number and percentage of subjects with serious TEAEs\*

- Number and percentage of subjects with serious study treatment-related TEAEs\*
- Number and percentage of subjects with TEAEs leading to death\*
- Number and percentage of subjects with study treatment-related TEAEs leading to death\*

#### **Summary of Adverse Events by SOC and PT:**

Those items marked with an asterisk (\*) above will be summarized by SOC, PT, and severity in each study part (core and extension) and overall, and the total number of events will also be included in the output.

#### **Summary of Adverse Events by PT:**

The following items will be summarized by PT and severity by descending order of frequency in each study part (core and extension) and overall.

- Number and percentage of subjects with any TEAE
- Number and percentage of subjects with a study treatment-related TEAE

#### **Summary of Adverse Events by onset time subgroups:**

The following items will be summarized by SOC, PT, and onset time subgroups in each study part (core and extension) and overall.

- Number and percentage of subject with any TEAE
- Number and percentage of subjects with a study treatment-related TEAE

#### **Subgroup analyses for Adverse Events:**

The subgroup analysis will be conducted with the subgroup factors listed in section 7.9. The following items will be summarized by SOC, PT, and severity in each study treatment group and overall in each study part (Core and Extension) and overall.

- Number and percentage of subjects with any TEAE
- Number and percentage of subjects with any study treatment-related TEAE
- Number and percentage of subjects with any serious TEAE
- Number and percentage of subjects with any study treatment-related serious TEAE.

#### **Deaths:**

A summary and listings of deaths will be provided. The number and percentage of subjects by study treatment group in each study part (core and extension) and overall, for all deaths regardless of date of death and, separately, deaths occurring within the period of treatment emergence (from the date of first administration of study treatment to 28 days after the last dose of ONO-2808), will be provided for the following categories:

- Total number of deaths
- Primary cause of death
- Adverse Event with outcome of death only
- Subjects with unknown reason of death

- Adverse Events of Special Interest (AESI):**

- At least one AESI by severity
- At least one study treatment-related AESI by severity
- At least one AESI leading to interruption of study treatment
- At least one study treatment-related AESI leading to interruption of study treatment
- At least one AESI leading to withdrawal of study treatment
- At least one study treatment-related AESI leading to withdrawal of study treatment
- At least one serious AESI
- At least one serious study treatment-related AESI
- At least one AESI leading to death
- At least one study treatment-related AESI leading to death



All items above will be summarized by category and PT.

## 17.3 Clinical Laboratory Evaluations

### 17.3.1 Analysis Items and Data Handling

The details of laboratory parameters are described in the study protocol. Both United States Conventional Units (CU) and International System (SI) units will be used in all outputs, with CU summaries appearing first.

Corrected calcium: Corrected calcium will be derived during creation of the reporting database using the following formula (Payne et al., 1973<sup>6</sup>):

US Conventional Unit:

$$\text{Corrected calcium (mg/dL)} = \text{Total calcium (mg/dL)} + 0.8 \times ([4 - \text{Albumin (G/dL)}])$$

SI unit:

$$\text{Corrected calcium (mmol/L)} = \text{Total calcium (mmol/L)} + ([40 - \text{Albumin (G/L)}] \times 0.02)$$

Creatinine Clearance: Creatinine Clearance will be derived using the Cockcroft-Gault formula (Cockcroft and Gault, 1976<sup>7</sup>) as below:

$$\text{Creatinine clearance (male)} = ([140 - \text{Age}] \times \text{Weight (kg)}) / (72 \times \text{Serum creatinine (mg/dL)})$$

$$\text{Creatinine clearance (female)} = ([140 - \text{Age}] \times \text{Weight (kg)}) / (72 \times \text{Serum creatinine (mg/dL)}) \times 0.85$$

For exploratory and comparison purposes, creatinine clearance will also be derived using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (Levey et al., 2009<sup>8</sup>) as below:

- Female and Serum creatinine (mg/dL)  $\leq 0.7$ :

$$\text{Creatinine clearance} = 141 \times (\text{Serum creatinine}/0.7)^{-0.329} \times (0.993)^{\text{Age}} \times 1.018 \times 1.159 [\text{if Black}]$$

- Female and Serum creatinine (mg/dL)  $> 0.7$ :

$$\text{Creatinine clearance} = 141 \times (\text{Serum creatinine}/0.7)^{-1.209} \times (0.993)^{\text{Age}} \times 1.018 \times 1.159 [\text{if Black}]$$

- Male and Serum creatinine (mg/dL)  $\leq 0.9$ :

$$\text{Creatinine clearance} = 141 \times (\text{Serum creatinine}/0.9)^{-0.411} \times (0.993)^{\text{Age}} \times 1.159 [\text{if Black}]$$

- Male and Serum creatinine (mg/dL)  $> 0.9$ :

$$\text{Creatinine clearance} = 141 \times (\text{Serum creatinine}/0.9)^{-1.209} \times (0.993)^{\text{Age}} \times 1.159 [\text{if Black}]$$

Age is in years.

### 17.3.2 Analysis Methods

Observed laboratory parameter results will be summarized along with change from baseline results in each study part (core and extension) and overall by time point, by study treatment group and overall, as applicable.

Hematology, clinical chemistry, urine quantitative, and coagulation data will be summarized (n, mean, median, SD, minimum, maximum) for each laboratory parameter at each time point, including changes from baseline in each study part (core and extension) at each scheduled post-baseline time point. At post-baseline time points, the baseline mean and SD for those subjects with non-missing data at both baseline and post-baseline will be additionally presented in each study part (core and extension). The number and percentage of subjects with abnormal laboratory results for selected parameters (see below) at any time during the study (including unscheduled visits) will be tabulated by parameter, study treatment group, and overall in each study part (core and extension) and overall.

The number and percentage of subjects in each category of urine qualitative data will be tabulated at each time point, in each study part (core and extension) and overall.

All hematology, clinical chemistry, urinalysis, and coagulation data including changes from baseline in each study part (core and extension) will be listed for all Enrolled subjects. In these listings, sample collection data for laboratory analysis and urinalysis data will be included, and individual data will be flagged with an “H” or an “L” for values that are higher or lower than their reference ranges, respectively. Serum or urine pregnancy test results, and alcohol will be listed along with other serology screening test results (HIV antibody, hepatitis B surface antigen [HBsAg], HCV antibody, and SARS-CoV-2).

For hematology and clinical chemistry data, shift tables will be provided for baseline categories of low/normal/high reference range results to post-baseline time point category results in each study part and overall. The following categories are defined for the shift tables:

- Low: Values which are below the lower reference range limit
- Normal: Values which are within the lower and upper reference range limits
- High: Values which are above the upper reference range limit

For hematology and clinical chemistry variables, tables presenting the changes from *Low* or *Normal* to *High*, and from *High* or *Normal* to *Low* will be provided by study part. In addition, a categorical summary of post-baseline clinically significant abnormal laboratory results, at any time including unscheduled visits, will be provided for each study part and overall.

Focusing on abnormal hepatic function, including potential Hy’s law cases, the frequency distributions of subjects who meet each of the criteria will be calculated for select laboratory parameters based upon the maximum post-baseline value achieved for each subject in each study part (core and extension) and overall. At a minimum, the following categories will be included:

- Aspartate aminotransferase (AST) >Upper Limit of Normal [ULN] and  $\leq 3 \times \text{ULN}$ ,  $> 3 \times \text{ULN}$  and  $\leq 5 \times \text{ULN}$ ,  $> 5 \times \text{ULN}$  and  $\leq 8 \times \text{ULN}$ ,  $> 8 \times \text{ULN}$  and  $< 10 \times \text{ULN}$ ,  $\geq 10 \times \text{ULN}$  and  $< 20 \times \text{ULN}$ ,  $\geq 20 \times \text{ULN}$
- AST  $> 3 \times \text{ULN}$ ,  $> 5 \times \text{ULN}$ ,  $> 8 \times \text{ULN}$ ,  $\geq 10 \times \text{ULN}$ , and  $\geq 20 \times \text{ULN}$
- Alanine aminotransferase (ALT)  $> \text{ULN}$  and  $\leq 3 \times \text{ULN}$ ,  $> 3 \times \text{ULN}$  and  $\leq 5 \times \text{ULN}$ ,  $> 5 \times \text{ULN}$  and  $\leq 8 \times \text{ULN}$ ,  $> 8 \times \text{ULN}$  and  $< 10 \times \text{ULN}$ ,  $\geq 10 \times \text{ULN}$  and  $< 20 \times \text{ULN}$ ,  $\geq 20 \times \text{ULN}$
- ALT  $> 3 \times \text{ULN}$ ,  $> 5 \times \text{ULN}$ ,  $> 8 \times \text{ULN}$ ,  $\geq 10 \times \text{ULN}$ , and  $\geq 20 \times \text{ULN}$

- [illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **17.4 Physical Examinations**

### **17.4.1 Analysis Items and Data Handling**

Physical examinations of the subjects will be performed as described in the study protocol.

### **17.4.2 Analysis Methods**

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant physical examination results will be tabulated by parameter at each time point and by study treatment group and overall in each study part (core and extension).

All physical examination data (i.e., skin, head, lymph nodes, thyroid, cardiovascular, abdomen, eyes, ears, nose, throat, neurological, lungs, extremities, and others) will be listed for all Enrolled subjects.

## **17.5 Vital Signs**

### **17.5.1 Analysis Items and Data Handling**

The details of measurements of vital sign variables are described in the study protocol. For the screening visit and selected timepoints (baseline, visit 10, visit 13, and end of termination (ET) in the core part, and visit 14, visit 21, visit 24, visit 26, visit 27, visit 28, visit 30, and ET in the extension part, the orthostatic vital signs (supine and then standing position) will be used for

measurements, and all other timepoints will use supine position. No imputation will be conducted for missing baseline data.

### **17.5.2 Analysis Methods**

Height and weight will be listed and summarized as a part of baseline characteristics. Vital signs data (i.e., systolic blood pressure, diastolic blood pressure, pulse rate, body temperature and respiratory rate) at each scheduled assessment, including changes from baseline in both positions in each study part (core and extension) and overall, will be listed and summarized using descriptive statistics by study treatment group and overall in each study part. At post-baseline time points, the baseline mean and SD for those subjects with non-missing data at both baseline and post-baseline in each study part will be additionally presented. All vital sign data will be listed for all Enrolled subjects.

A categorical summary of post-baseline clinically significant abnormal vital sign results, at any time, including unscheduled visits, will be provided for each study part and overall.

## **17.6 12-Lead ECGs**

### **17.6.1 Analysis Items and Data Handling**

The details of measurements of ECG parameters are described in the study protocol. The arithmetic mean of the non-missing triplicate values for each 12-lead ECG measurement will be derived and used for listings and summaries. Where triplicate measurements have been taken, the changes from baseline in each study part (core and extension) will be calculated using the arithmetic mean values only.

Corrected QT intervals based on Fridericia's and Bazett's (QTcF and QTcB, respectively) formula's will be calculated using the following equations:

- $QTcF = QT / [RR/1000]^{1/3}$
- $QTcB = QT / [RR/1000]^{1/2}$

The unit of QTcF, QTcB, QT, and RR in the above formulas is milliseconds (ms).

### **17.6.2 Analysis Methods**

ECG parameters (heart rate, RR, PR interval, QT interval, corrected QT interval using Fredericia's formula [QTcF], corrected QT interval using Bazett's formula [QTcB], and QRS), including changes from baseline in each study part (core and extension) and overall, will be summarized using descriptive statistics at each scheduled time point. At post-baseline time points, the baseline mean and SD for those subjects with non-missing data at both baseline and post-baseline will be additionally presented in each study part.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results will be tabulated at each time point in each study part. If different ECG interpretations are available, the majority rule will be applied to determine the ECG results used for analysis (e.g. if two normal results and one abnormal not clinically significant result were available, normal will be used for analysis).

In addition, the highest post-baseline QTcF absolute value and change from baseline values calculated from these values from each subject in each study part will be summarized by study treatment group and overall, and by study part and overall, in terms of frequencies and percentages within the following categories:

- QTcF (ms)
  - $\leq 450$
  - $450 - \leq 480$
  - $480 - \leq 500$
  - $500$
- Increase from baseline of QTcF (ms)
  - $\leq 30$
  - $30 - \leq 60$
  - $60$
- QTcF (ms) and increase from baseline of QTcF (ms)
  - $450$  and increase  $> 30$
  - $500$  and increase  $> 60$

These categories will be repeated for QTcB (ms).

Overall evaluation of ECG is also collected at each visit in terms of normal or abnormal, and the relevance of the abnormality is categorized as “clinically significant (CS)” or “not clinically significant (NCS)”, but this information will not be summarized as the above ECG read information is considered more clinically interpretable.

All ECG data, including changes from baseline in each study part, will be listed and clinical interpretation (normal, abnormal NCS and abnormal CS) will be listed for all Enrolled subjects. These listings will include the individual triplicate values and the calculated arithmetic mean value where appropriate.

## **17.7 Columbia Suicide Severity Rating Scale**

### **17.7.1 Analysis Items and Data Handling**

Subjects being treated with ONO-2808 will be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes (e.g., placebo group transitioned to 5 mg of ONO-2808 in the extension part).

Baseline assessment of SIB/intervention-emergent will be monitored during the study using the Columbia Suicide Severity Rating Scale (C-SSRS<sup>4</sup>).

The following outcomes are C-SSRS questions and have binary responses (Yes/No):

1. Question 1: Wish to be Dead.
2. Question 2: Non-specific Active Suicidal Thoughts

3. Question 3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4. Question 4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5. Question 5: Active Suicidal Ideation with Specific Plan and Intent
6. Question 6: Actual Attempt
7. Question 7: Engaged in Non-Suicidal Self-Injurious Behavior
8. Question 8: Interrupted Attempt
9. Question 9: Aborted Attempt
10. Question 10: Preparatory Acts or Behavior
11. Question 11: Suicidal Behavior
12. Question 12: Suicide (Asked only Since-Last-Visit C-SSRS)

Endpoints based on the above questions are defined below:

- Suicidal ideation: A “Yes” answer at any time during the study to any one of the five suicidal ideation questions (Questions 1-5) on the C-SSRS
- Suicidal behavior: A “Yes” answer at any time during the study to any one of the seven suicidal behavior questions (Questions 6-12) on the C-SSRS
- Suicidal ideation or behavior: A “Yes” answer at any time during the study to any one of the twelve suicidal ideation and behavior questions (Questions 1-12) on the C-SSRS

The C-SSRS will be assessed in clinic at screening, Visit 1 (baseline), Visit 10 (Week 12), Visit 13 (Week 24) and the ET visits in the core part. For the extension part, the C-SSRS will be assessed at Visit 14 (Week 32), Visit 21 (Week 40), Visit 24 (Week 48), Visit 26 (Week 56), Visit 27 (Week 68), Visit 28 (Week 80), Visit 30 (Week 92), and the ET visit.

Two versions of C-SSRS will be used in this trial: the Baseline/Screening C-SSRS with evaluation time of lifetime and past 12 months (lookback times) at Screening and Baseline visits, and Since-Last-Visit C-SSRS (the assessment will be based on from the prior visit) at all follow-up visits. A clinically abnormal finding of C-SSRS is defined as at least one question with a “Yes” answer. Missing data will not be imputed, and the results will be based on non-missing responses.

### 17.7.2 Analysis Methods

The number and percentage of subjects with any of the three endpoints that are defined as a clinically abnormal finding (suicidal ideation, suicidal behavior, and suicidal ideation or behavior), will be tabulated at each time point by study part (Core and extension) and overall.

A shift table will present changes from pre-treatment to any post-first-dose time point, with the number and percentage of subjects showing a worsening from baseline on any of the three clinically abnormal endpoints, for each study part and overall. Subjects with both suicidal ideation and suicidal behavior will be included in the suicidal behavior as each subject is counted in one category only. Shift tables will be analyzed in two ways:

- i. Shifts from baseline, where C-SSRS is relative to subject recall of the lifetime using the Baseline/Screening C-SSRS, to each post-baseline time point.

- ii. Shifts from baseline, where C-SSRS is relative to subject recall of the past 12 months using the Baseline/Screening C-SSRS, to each post-baseline time point.

A listing of all C-SSRS data will be provided for all Enrolled subjects, while a listing of subjects who demonstrated worsening on any of the three clinically abnormal endpoints will also be provided.

## 18 PHARMACOKINETICS

### 18.1 Analysis Items and Data Handling

Plasma pharmacokinetics (PK) sampling will be collected at before daily dose during Visit 3 (Week 2) and Visit 8 (Week 8) [REDACTED] and at before daily dose,  $3h \pm 1h$ , and  $5h \pm 1h$  post daily dose during Visit 10 (Week 12) and Visit 13 (Week 24) [REDACTED] (see Protocol [Section 8.5 Pharmacokinetics](#)).

When no date and/or time point of administration are recorded for PK analysis: Administration is determined not to have been performed appropriately. Therefore, the PK concentration values collected at time points relative to the administration which has the missing date/time information will not be included in any PK concentration summaries.

When no sampling time is recorded for PK analysis: Sampling is determined not to have been performed appropriately. Therefore, the PK concentration values will not be included in any PK concentration summaries.

Handling the below the lower limit of quantification (BLQ) in PK analysis: BLQ data will be assigned a value of zero in any PK concentration summary.

If less than 2 subjects have a quantifiable value at a nominal time point, then the descriptive statistics, except the n, min and max, will not be presented. All BLQ values will be presented as “BLQ” in the PK concentration listings.

Handling anomalous values in PK analysis: Any anomalous concentration values will be identified. Such anomalous concentration values will be included in listings but not included in descriptive statistics. Justification for this exclusion will be provided in the CSR

### 18.2 Analysis Methods

The PK analysis will be based on PKs. PK assessments will not be performed in the extension part of this study.

A subject listing of all available ONO-2808 concentration-time data for each dose level/day/scheduled time will be presented.

The plasma concentrations of ONO-2808 will be summarized using descriptive statistics (n, mean, SD, CV%, median, minimum, maximum, geometric mean, geometric CV% and geometric n) at each scheduled evaluation time point for each visit day and each study treatment group. Summaries of the summary statistics for plasma concentrations will be reported to 3 significant figures, except for CV% which will be presented with 1 decimal place and for n and geometric n which will be presented with integer. Any data to be excluded from the PK concentrations summary statistics will be included in the PK concentration listing and flagged.

## **19 PHARMACODYNAMICS/BIOMARKERS**



## 20 SUBJECT REPORTED OUTCOME ASSESSMENTS

Clinical outcome assessments include the UMSARS, [REDACTED] and are considered exploratory efficacy endpoints.

For each subscale of the questionnaires/assessments (UMSARS, [REDACTED]), if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items will be treated as missing. The reason for any missing questionnaire items will be identified and recorded. If there is evidence that the missing data are systematic (rather than missing at random), missing values will be handled to ensure that any possible bias is minimized. Change from baseline values in each study part and overall will be derived for each subscale/item, as appropriate.

### 20.1 Unified Multiple System Atrophy Rating Scale

#### 20.1.1 Analysis Items and Data Handling

UMSARS measures disease progression in MSA. The UMSARS consist of four subscales:

- Historical review rates patient-reported functional disability based on 12 items (speech, swallowing, handwriting, cutting food and handling utensils, dressing, hygiene, walking, falling, orthostatic symptoms, urinary function, sexual function, and bowel function) graded on a scale from 0-4.
- Motor examination assesses motor impairment based on a clinical examination based on 14 items (facial expression, speech, ocular motor dysfunction, tremor at rest, action tremor, increased tone, rapid alternating movements of hands, finger taps, leg agility, heel-knee-shin test, arising from chair, posture, body sway, and gait) graded on a scale from 0- 4.

[REDACTED]

[REDACTED]

The UMSARS is administered at screening, Visit 1 (baseline), Visit 10 (Week 12), Visit 13 (Week 24), and the early termination (ET) visit in the core part. For the extension part, the UMSARS will be administered at Visit 14 (Week 32), Visit 21 (Week 40), Visit 24 (Week 48), Visit 26 (Week 56), Visit 27 (Week 68), Visit 28 (Week 80) and the ET visit. The total scores for the historical review subscale and motor examination subscale will be calculated by summing the scores for the relevant items. The UMSARS-1 score will be the total score for historical review (12 items) and the UMSARS-2 score will be the total scores for motor examination (14 items). The UMSARS total score will be calculated as the sum of the total scores for historical review and motor examination (UMSARS total score = UMSARS-1 + UMSARS-2). Additionally, UMSARS-3 score will be calculated by summing the scores for the historical review items without Item 11 (Sexual function) (11 items). The UMSARS-1 score ranges from 0-48 points, the UMSARS-2

score ranges from 0-56 points, the UMSARS-3 score ranges from 0-44 points, and the UMSARS total score ranges from 0-104 points, with higher scores indicating greater severity of impairment.

Additionally, the modified UMSARS score will be calculated as the sum of the subset of items from historical review and motor examination subscales. The items in the modified UMSARS score will include the following historical review subscale items: speech, cutting food and handling utensils, dressing, hygiene, walking, and urinary function. The following motor examination subscale items will also be included: arising from chair, posture, and gait. In the analysis of all items, the response categories of 0 and 1 will be combined into a single category of 0 and subsequent scores recoded from 2 to 1, 3 to 2, and 4 to 3, reducing the range of scoring options from 0 to 3, before summing the individual items to derive the modified UMSARS score. The modified UMSARS score ranges from 0-27 points (a total of 9 items on scale of 0-3) with higher scores indicating greater severity of impairment.

The UMSARS compliance rate will be calculated at each visit and overall (i.e. across all visits) for each subject in each study part (core and extension) and overall and is defined as number of evaluable questionnaires (a questionnaire with a date and at least one non-missing subscale) divided by number of expected questionnaires (a questionnaire that is expected to be completed given the patient status on the study) expressed as a percentage.

### **20.1.2 Analysis Methods**

Each rating scale item, historical review subscale score (UMSARS-1), motor examination subscale score (UMSARS-2), autonomic examination (systolic and diastolic blood pressures and heart rate in the supine and standing positions), UMSARS-3 score, UMSARS total score, and global disability scale will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum for continuous variables, and frequency and percentage for categorical variables) at each time point, including changes from baseline at each scheduled post-baseline time point by study treatment group and overall in each study part (core and extension) and overall. At post-baseline time points, the baseline mean and SD for those subjects with non-missing data at both baseline and post-baseline will be additionally presented. All individual UMSARS-1, UMSARS-2, UMSARS-3, UMSARS total scores, modified UMSARS total scores, systolic and diastolic blood pressures, and heart rate in the supine and standing positions (autonomic examination subscale) will be plotted with lines connecting values from the same subject (spaghetti plots).

Longitudinal models will be explored to estimate the change in historical review subscale score (UMSARS-1), motor examination subscale score (UMSARS-2), UMSARS-3, UMSARS total score, and modified UMSARS score, as well as systolic and diastolic blood pressures and heart rate in the supine and standing positions (autonomic examination subscale) at each time point, as appropriate. A linear mixed-effect model will include the fixed categorical effects of time point and study treatment group as well as time point and study treatment group interaction and subject as random effect for intercept will be applied. An unstructured variance-covariance matrix will initially be assumed to model the within-subject correlations (Type='UN' in the REPEATED statement in PROC MIXED procedure in SAS). If this model does not converge, a heterogeneous Toeplitz (Type='TOEPH') will be first used and then a first order auto-regressive (AR(1)) structure (Type='AR(1)') will be used. If the model using a heterogeneous Toeplitz or AR(1) structure does not converge, the model will use a compound symmetry structure (Type='CS') which assumes equal correlation for subjects' measurements, regardless of how far apart in time they were taken. The Kenward-Roger approximation will be used to estimate denominator degrees

For each item of the historical review and motor examination subscales, the number and percentage of subjects who reported “0”, “1”, “2”, “3”, and “4” at each time point will be calculated. [REDACTED]

A listing of UMSARS item/scale results will be provided for all Enrolled subjects

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## 21 INTERIM ANALYSIS

An interim analysis is planned after the last subject from the core part of the ONO-2808-03 study completes V13 (Week 24). All safety and exploratory efficacy endpoints will be included in the interim analysis, which will include comparison of changes from baseline of the core part. At the time of the interim analysis, some of the subjects will still be in the extension part. The primary focus of the interim analysis will be the core part of the study. Therefore, all available safety and efficacy endpoints for the core part only will be included in the interim analysis. Results from the interim analysis will be used for planning future trials for ONO-2808.

All safety endpoints (AEs, deaths, clinical laboratory evaluations, physical examinations, vital signs, 12-Lead ECGs, C-SSRS, and other safety analysis) will be analyzed as described in section 17.

UMSARS is an important exploratory efficacy endpoint and will be analyzed as described in section 20.1. [REDACTED]

[REDACTED] will be analyzed as described in section 20.

For the timing of the primary analysis, see section 4.

### Independent Data Monitoring Committee

This study will use an [REDACTED] IDMC [REDACTED]

[illegible]

## **22      CHANGES FROM THE PLANNED ANALYSES DEFINED IN THE          PROTOCOL**

Not applicable for this version of SAP.

## 23 REFERENCES

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## APPENDIX 1

### Missing date imputation rules

An imputation of end date should be performed before an imputation of start date.

If a start date is partial or missing, then use the following imputation rules (references to year and month refer to the year and month of the start date, respectively):

1. If year and month are known, and it is the month of the first study medication dose date and the end date is prior to the first dose date, use the first day of the month.
2. If year and month are known, and it is the month of the first study medication dose date and the end date is the same as or later than the first dose date, use the first dose date.
3. If year and month are known, and it is any month following the first study medication dose date, use the first day of the month.
4. If year and month are known and it is any month prior to first study medication dose date, use the first day of the month.
5. If only year is known, and it is previous to the year of the first study medication dose date, use June 30th of that year. If it is the same as the first dose date year, assume it is the first dose date. If it is later than the first dose date year, assume it is the first day of the year.
6. If a start date is completely missing, but an end date is known or partial, use the first study medication dose date.
7. Should any of the previous start dates that were created be after a known end date, use the end date instead of the date that would otherwise be created.

If an end date is partial or missing, then use the following imputation rules (references to year and month refer to the year and month of the end date, respectively):

1. If year and month are known and study medication ended during that month, use the end date of study medication.
2. If year and month are known and study medication ended after that month, use the last day of the month.
3. If year and month are known and study medication ended prior to that month, use the first day of the month.
4. If only year is known, and it is the same as last study medication dose date year, assume it is the last dose date. If it precedes the last dose date year, assume it is the last day of the year. If it is later than the last dose date year, assume it is the first day of the year.
5. If an end date is completely missing, but a start date is known or partial, or “ongoing” is checked, set to date of last study medication dose date.
6. Should any of the previous end dates that were created come before a start date, either a known date or an imputed one, use the start date instead of the date that would otherwise be created.