

STUDY PROTOCOL

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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Sponsor Name:

Ono Pharmaceutical Co., Ltd.

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CLINICAL STUDY PROTOCOL

Protocol 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)

Protocol Number:

ONO-2808-03

Version Number:

Version 6.0

Compound:

ONO-2808

Brief Title:

A Phase 2 study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and potential efficacy of multiple doses of ONO-2808 in patients with MSA

Study Phase:

Phase 2

Sponsor Name:

Ono Pharmaceutical Co., Ltd.

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Protocol No.: ONO-2808-03

Version No.: 6.0

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance/adherence with the ethical principles originating in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or an Institutional Review Board/Independent Ethics Committee (IRB/IEC).

Principal Investigator

Date

Name (Signature)

Site number

(Printed name)

I hereby confirm and approve the clinical study protocol mentioned above. I also hereby assume the responsibility of conducting and managing the clinical study in accordance with the terms of this protocol.

Company Representative

<Refer to the electronic signature page>

Date

[REDACTED]
[REDACTED]
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LIST OF ABBREVIATIONS

Term	Definition
ADL	Activities of daily living
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibody
ANA	Anti-nuclear antibody
ApoM	Apolipoprotein M
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AT	Aminotransferase
ATP	Adenosine triphosphate
AxMP	Auxiliary medicinal product
β-hCG	Urine beta human chorionic gonadotrophin
BUN	Blood urea nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CMV	Cytomegalovirus
COA	Clinical outcome assessment
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Event
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

Term	Definition
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
FIH	First-in-Human
FSH	Follicle-Stimulating Hormone
■	■
GCP	Good Clinical Practice
■	■
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDFU	Investigational directions for use
IDMC	Independent Data Monitoring committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
■	■
ITT	Intention-To-Treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LAR	Legally-authorized representative
LDH	Lactate dehydrogenase
LFT	Liver Function Test
■	■

Term	Definition
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
PT	Prothrombin time
QTcF	QT interval corrected using Fridericia's formula
S1P	Sphingosine-1-phosphate
S1PR5	Small molecule sphingosine-1-phosphate receptor-5
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard deviation
SGPT	Serum glutamic-pyruvic transaminase
SIB	Suicidal ideation and behavior
SoA	Schedule of Activities
SOC	Standard of care
SRC	Study Review Committee
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UMSARS	Unified Multiple System Atrophy Rating Scale
WOCBP	Woman of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol 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)

Brief Title:

A Phase 2 study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and potential efficacy of multiple doses of ONO-2808 in patients with MSA.

Regulatory Agency Identifier Number(s):

IND 162824

Rationale:

Based on its mechanism of action, ONO-2808 has the potential to provide symptomatic improvement and modify disease progression in patients with MSA by promoting remyelination and reducing pathogenic CNS α -synuclein accumulation. This initial study of ONO-2808 in MSA patients will generate data to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and potential efficacy of 3 doses of ONO-2808 compared to placebo.

Objectives and Endpoints:

The following objectives and endpoints are applicable to the core, the extension, and the additional extension parts of the study, unless indicated.

Objectives	Endpoints
Primary Objective	Primary Endpoint
• To evaluate the safety and tolerability of multiple oral doses of ONO-2808 in patients with MSA	• Incidence or change from the baseline in the following assessments: ○ Incidence and severity of adverse events (AEs) ○ Vital signs (blood pressure, pulse rate, temperature, respiratory rate) ○ 12-lead electrocardiograms (ECGs); parameters such as, but not limited to, heart rate, RR, PR, QRS, QT, and corrected QT intervals (QTcF)

	○ Clinically-significant abnormal physical examination findings ○ Clinically-significant laboratory abnormalities (hematology, clinical chemistry, and urinalysis), including survey of drug-induced liver abnormalities ○ Clinically-abnormal findings in Columbia Suicide Severity Rating Scale (C-SSRS)
Secondary Objectives	Secondary Endpoints
• To evaluate the pharmacokinetics (PK) of multiple oral doses of ONO-2808 in patients with MSA	• Plasma concentration of ONO-2808 (core part only)
Exploratory	Exploratory Endpoints
• To evaluate performance of clinical outcome assessments (COA) in patients with MSA taking multiple doses of ONO-2808	• Change from baseline in the following assessments: ○ Unified Multiple System Atrophy Rating Scale (UMSARS) ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED]
• [REDACTED]	• [REDACTED] ■ [REDACTED] ■ [REDACTED]

• To evaluate performance of imaging biomarkers in patients with MSA taking multiple doses of ONO-2808	• Imaging parameters may include, but are not limited to: ○ Magnetic resonance imaging (MRI) volumetric assessments of white and gray matter ○ Diffusion tensor imaging (DTI) for white matter abnormalities (core part and extension part only)
--	--

Overall Design Synopsis:

Study ONO-2808-03 is a Phase 2, double-blind, parallel-group, placebo-controlled study to assess the safety, tolerability, PK, PD, and efficacy of multiple doses of ONO-2808 in patients with 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, participants 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 (COA) 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 participants will be randomized to ensure [REDACTED]. Eligible participants 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. Participants will receive blinded study treatment orally once daily (QD) for 24 weeks and will be followed up for 4 weeks after treatment discontinuation. At the end of treatment in the core part, patients may continue receiving treatment in an extension part of this study. [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 Columbia Suicide Severity Rating Scale (C-SSRS). [REDACTED] Clinical outcome assessments to be performed include the Unified Multiple System Atrophy Rating Scale (UMSARS), [REDACTED] and brain and liver magnetic resonance imaging (MRI).

[REDACTED]

Standard of care (SOC) treatments for MSA consistent with local medical practice will be allowed during the study.

Extension Part and Additional Extension Part:

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

The purpose of this extension part is to evaluate 3 doses of ONO-2808 in MSA patients, 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.

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

Participants who complete EOT/V28 in the extension part above will be eligible to rollover into an additional extension part. Participants who rollover into this additional extension part will continue the same dose assignment from the extension part. The treatment duration in this additional extension part will vary by participant and is expected to be up to approximately 48 to 72 weeks, depending on the timing of rollover [REDACTED]. All participants 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.

SOC treatments for MSA consistent with local medical practice will be allowed during the study.

Brief Summary:

Core Part:

The purpose of this study is to evaluate the safety, tolerability, PK, PD, and potential efficacy of multiple doses of ONO-2808 in patients with MSA.

ONO-2808 is a novel, oral, small molecule sphingosine-1-phosphate receptor-5 (S1PR5) agonist that is being developed for the treatment of MSA. Based on its mechanism of action, ONO-2808 has the potential to provide symptomatic improvement and modify disease progression in patients with MSA by promoting remyelination and reducing pathogenic CNS α -synuclein accumulation.

Potential participants will undergo a screening period of up to 6 weeks. Eligible participants will be assigned to receive 1 of 3 daily 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 participants, followed by a 4-week follow-up period after treatment discontinuation. [REDACTED]

After the completion of treatment in the core part, participants who continue to meet the relevant eligibility criteria and are willing to continue dosing will rollover to the extension part.

Extension Part and Additional Extension Part:

The purpose of this extension part is to evaluate the safety, tolerability, PD, and potential efficacy of long-term administration of ONO-2808 in patients with MSA.

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

Participants who complete EOT/V28 in the extension part above will be eligible to rollover into an additional extension part. Participants who rollover into this additional extension part will continue the same dose assignment from the extension part. The treatment duration in this additional extension part will vary by participant and is expected to be up to approximately 48 to 72 weeks, depending on the timing of rollover [REDACTED]. All participants will receive study treatment orally once daily (QD) and will be followed up for 12 weeks (follow-up period) after treatment discontinuation. [REDACTED]

[REDACTED]

Core, Extension, and Additional Extension Parts:

In all parts of the study, liver function will be specifically examined, in response to a limited number of transaminitis events seen during Phase 1 studies of ONO-2808 in healthy volunteers. Participants will continue to be instructed to report any DILI-related signs and symptoms during treatment administration. Participants should seek immediate medical attention if any DILI-related symptoms occur in trial participants either during the treatment period or up to 60 days after receiving the last dose of investigational agent or placebo.

The results from this extension part will also inform the identification of the primary endpoint, sample size, optimal ONO-2808 dose, and design of future clinical studies.

SOC treatments for MSA consistent with local medical practice will be available to all participants during this extension part.

Number of Participants:

Core Part:

A total of approximately 80 participants who have been diagnosed with MSA will be randomized into 4 treatment arms in this study. The sample size accounts for a [REDACTED] drop-out rate, resulting in [REDACTED] completed participants per treatment arm.

Extension Part and Additional Extension Part:

Participants who have completed the core part of ONO-2808-03 study may be enrolled in the extension part. Participants who have completed EOT/V28 in the extension part may subsequently be enrolled in the additional extension part.

Study Arms and Duration:

Core Part:

A total of approximately 80 participants will be randomized in a 1:1:1:1 ratio to one of 4 treatment arms [REDACTED]

Potential participants will undergo a screening period of up to 6 weeks. Eligible participants 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

participants. After the completion of treatment, participants who continue to meet the relevant inclusion/exclusion criteria and are willing to continue dosing will rollover to the extension part. The participants who are early discontinued from the core part or who will not enroll into the extension part will have a safety follow-up for 4 weeks after treatment discontinuation.

Extension Part and Additional Extension Part:

The extension part of the ONO-2808-03 study is an open-label and parallel-group study to assess the safety, tolerability, PD, and potential efficacy of the long-term administration of ONO-2808, with a target of up to 80 completers from the core part to rollover to this extension part.

Participants who were randomized in to one of 4 treatment arms in the core part will continue their treatment assignment for 8 weeks (rollover period) in this extension part. After freezing CRFs in the core part, participants assigned to placebo control treatment in the core part (placebo group) will be [REDACTED] ONO-2808 for 48 weeks (open-label treatment period). Participants on ONO-2808 doses (active groups) will continue their same ONO-2808 dose for the entirety of the open-label treatment period (48 weeks). All participants will be treated in an unblinded manner for this 48-week open-label treatment period in this extension part. All participants will receive study treatment orally once daily (QD) and will be followed up for 12 weeks (follow-up period) after treatment discontinuation.

In the additional extension part, participants will continue the same dose assignment from the extension part. The treatment duration in this additional extension part will vary by participant and is expected to be up to approximately 48 to 72 weeks, depending on the timing of rollover [REDACTED]. All participants will be treated in an unblinded manner in this additional extension part. All participants will receive study treatment orally once daily (QD) and will be followed up for 12 weeks (follow-up period) after treatment discontinuation.

Core, Extension and Additional Extension Parts:

Dose modifications for participants are not allowed during the study. If a participant experiences AEs that meet the individual stopping criteria during treatment with ONO-2808, the participant will be discontinued from further treatment, and followed for safety outcomes.

This study will proceed as planned, unless temporarily halted or stopped by the Sponsor of its own opinion or on the recommendation of the IDMC, IRB/IEC or competent health authority, after consideration of all available safety data and with reference to the stopping rules as defined in [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 patient 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.

Data Monitoring/Other Committee:

An IDMC will be appointed for this study. The IDMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human subject research study, and to make recommendations to the Sponsor regarding the stopping of a study due to safety concerns or lack of efficacy. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

1.2 Schema

Figure 1.2-1: Study Design, Core Part

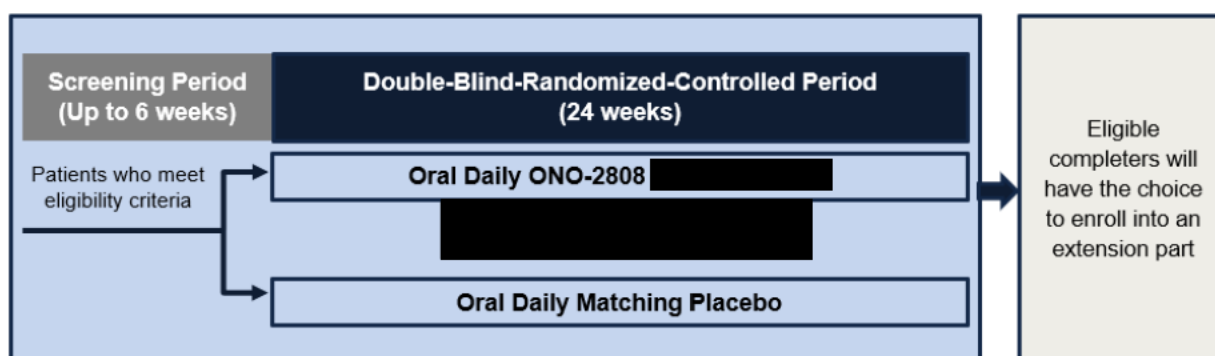


Figure 1.2-2: Study Design, Extension Part

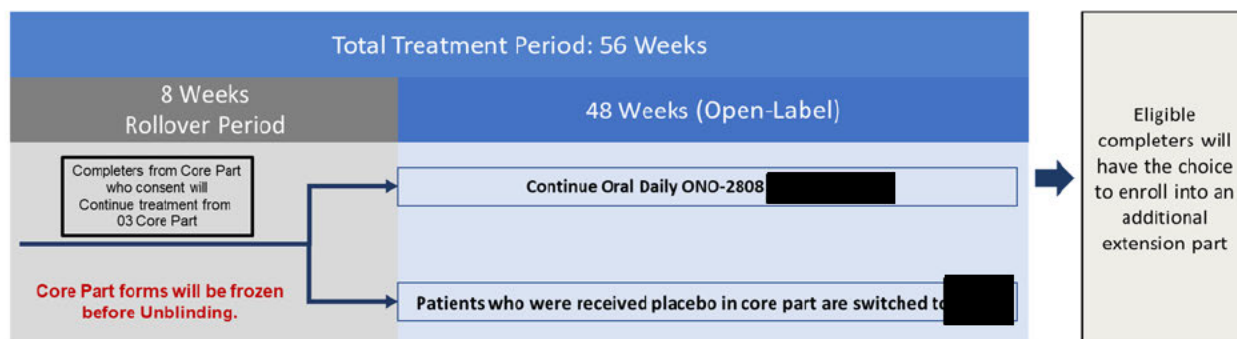


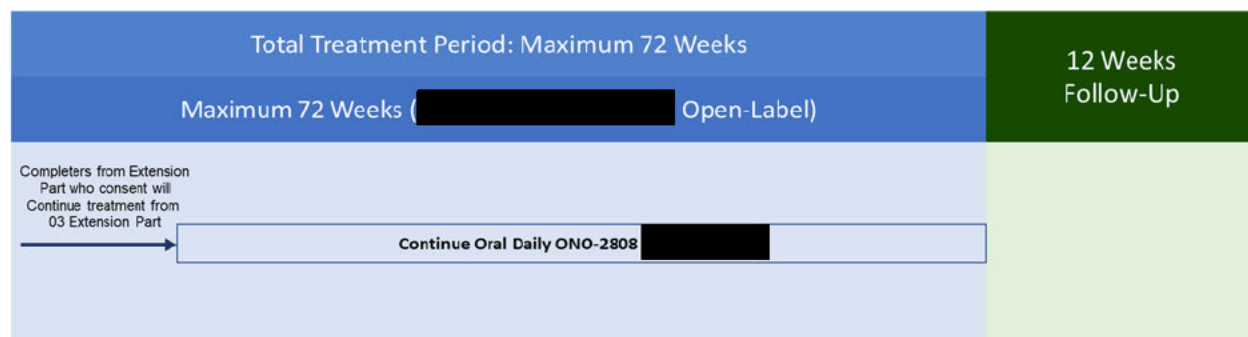
Figure 1.2-3: Study Design, Additional Extension Part

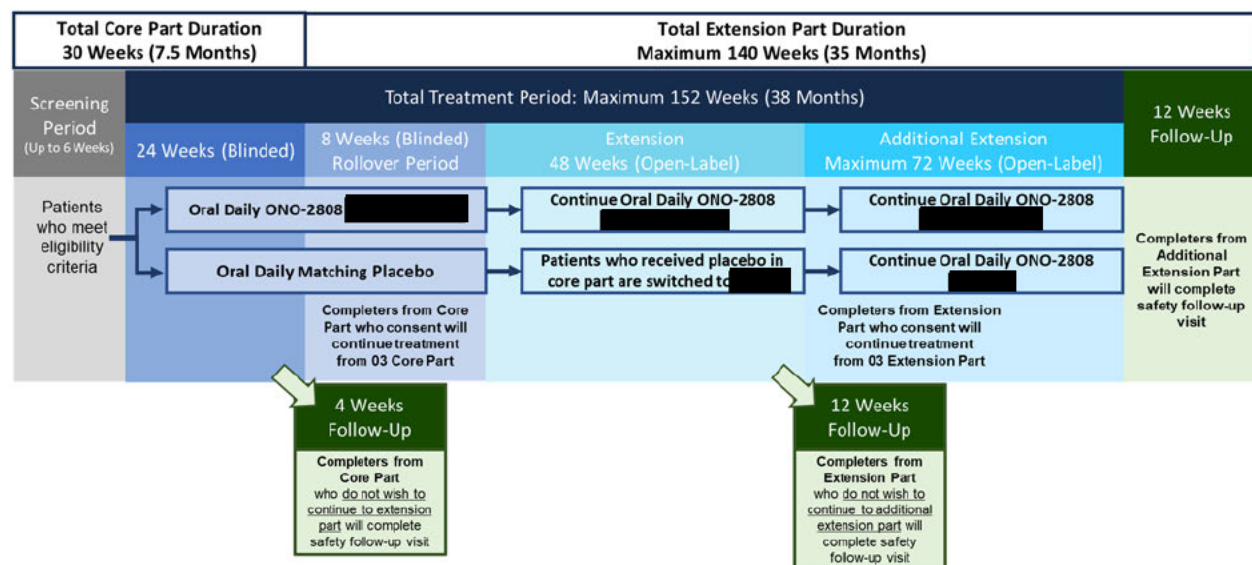
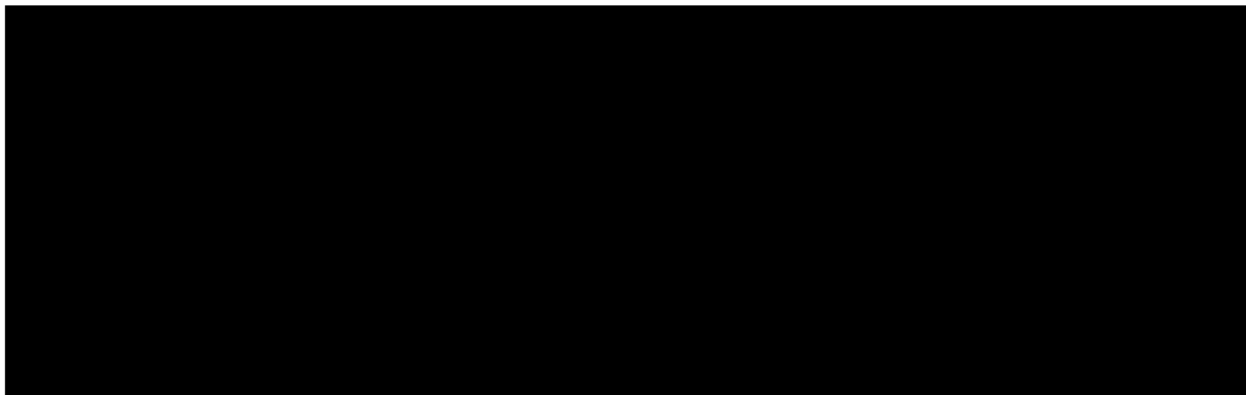
Figure 1.2-4: Overall Study Design**Figure 1.2-5: Study Flow, Core Part**

Figure 1.2-6: Study Flow, Extension Part

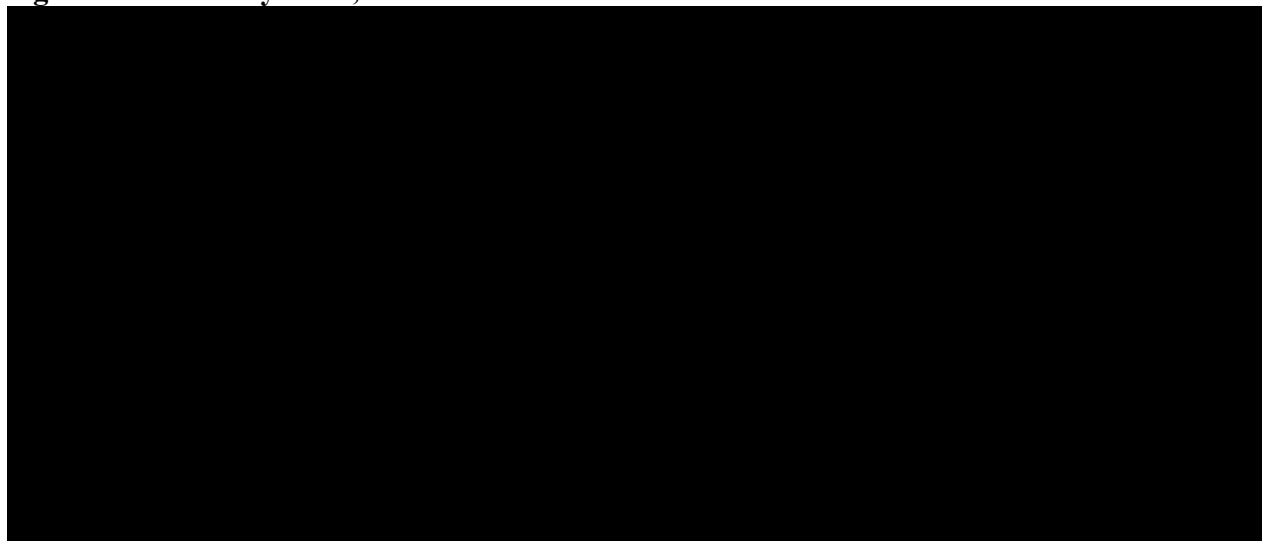
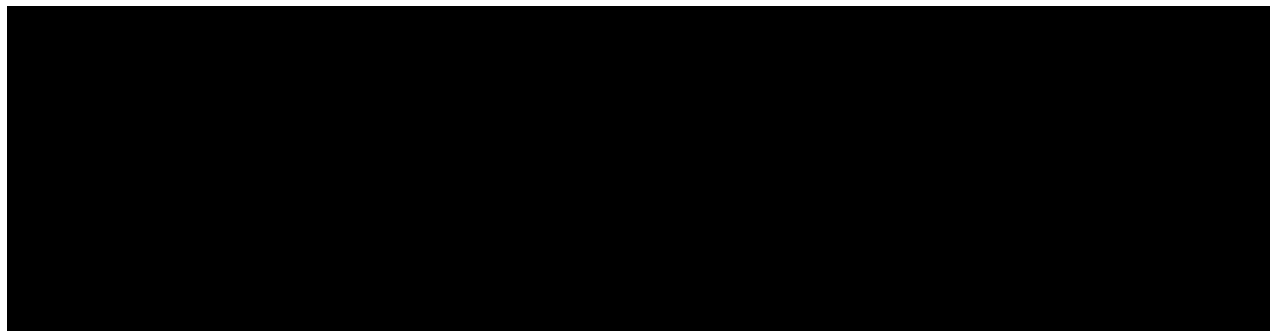


Figure 1.2-7: Study Flow, Additional Extension Part



1.3 Schedule of Activities (SoA)

Table 1.3-1: Schedule of Activities, Core Part

Visit Name	Screening ¹	Baseline V1 ¹		V2	V3	V4	V5	V6	V7	V8	V9	V10 ¹	V11	V12	EOT V13 ^{1,12}	FU ¹²	UNS ¹	ET ^{1,12}
Time of Visit	(-W6)	W0		W1	W2	W3	W4	W5	W6	W8	W10	W12	W16	W20	W24	W28		
		Day -2~-1	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 56	Day 70	Day 83~84	Day 112	Day 140	Day 167~168	Day 196		
Visit Window				±1d	±1d	±1d	±1d	±1d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Administrative Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Demographics ² , Medical History, and MSA Medication History	X	X																
Concomitant Treatments	X	X														X	X	X
Randomization		X																
Clinical Procedure/Assessments																		
Study Intervention Administration				Oral dosing once daily (QD)														
	X		X	X	X													
Adverse Events	X	X														X	X	X
Height	X																	
Vital Signs, Weight	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic Blood Pressure	X	X										X			X		X	X
Full Physical, and Neurological Exam	X	X										X			X			X
Brief Physical Exam ⁴				X	X	X	X	X	X	X	X		X	X		X	X	
12-Lead ECG	X	X		X	X		X			X		X	X	X	X	X		X
Laboratory Procedures/Assessments																		
Serology (HIV, HBV, HCV, SARS-CoV-2 ¹⁰)	X	X																
Chemistry Panel Including Kidney, Liver Function Tests, and Coagulation	X	X		X	X ⁵	X ⁵	X	X ⁵	X ⁵	X	X ⁵	X	X	X	X	X	X ⁵	X

Visit Name	Screen ing ¹	Baseline V1 ¹		V2	V3	V4	V5	V6	V7	V8	V9	V10 ¹	V11	V12	EOT V13 ^{1, 12}	FU ¹²	UNS ¹	ET ^{1, 12}	
Time of Visit	(-W6)	W0		W1	W2	W3	W4	W5	W6	W8	W10	W12	W16	W20	W24	W28			
		Day -2~-1	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 56	Day 70	Day 83~84	Day 112	Day 140	Day 167~168	Day 196			
Visit Window				±1d	±1d	±1d	±1d	±1d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d			
Hematology (CBC with Differential)	X	X		X			X			X		X	X	X	X	X	X	X	
Urinalysis ⁶	X	X		X			X			X		X	X	X	X	X	X	X	
Pregnancy Test (Urinary)	X	X		Monthly pregnancy testing as per local regulations where applicable												X		X	
PK and Biomarker Sampling (Plasma)																			
PK Sampling (Plasma) ⁷					X					X		X			X			X	
		X										X			X			X	
															X			X	
		X													X			X	
		X													X			X	
		X		X	X	X	X		X	X		X	X	X	X				
Clinical Outcomes Assessments/Brain and Liver Imaging																			
UMSARS	X	X										X			X			X	
		X										X			X			X	
		X										X			X			X	
		X													X			X	
	X																		
	X	X										X			X			X	
		X										X			X			X	
		X										X			X			X	
		X										X			X			X	
C-SSRS	X	X										X			X			X	
Brain MRI ⁹	X														X			X	
Liver MRI ⁹	X			As needed if persistent transaminitis is observed												X			X

Abbreviations [REDACTED]; C-SSRS=Columbia Suicide Severity Rating Scale; d=day; [REDACTED]; [REDACTED]
ECG=electrocardiogram; EOT=End of Treatment; ET=early termination; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; m=minute(s); [REDACTED]
[REDACTED]; PK=pharmacokinetic; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; [REDACTED]
[REDACTED] UMSARS = Unified Multiple System Atrophy Rating Scale; UNS=unscheduled visit; V=visit; W=week.

2. Demographics: age, race, ethnicity, and sex.

6. Urinalysis includes pH, bilirubin, ketones, nitrites, glucose, leucocytes, protein, urobilinogen, and blood.

8.

9. Brain and Liver MRI scanning can be combined; imaging studies may be performed once the principal investigator confirms eligibility based on screening visit examination and safety work-up. It is the responsibility of the Principal Investigator to review the formal central reading of the imaging studies to ascertain final eligibility towards randomization. It is preferred that the baseline MRI scanning be completed within 2 weeks prior to the start of dosing, however 4 weeks prior to the start of dosing is permitted.

10. SARS-CoV-2 testing will be optional per site policy and performed locally.

12. If IP discontinuation criteria are met due to elevated LFTs:

- An End of Treatment (EOT) Visit should be conducted as soon as possible

- A Safety Follow-up Visit should be conducted 4 weeks after IP is discontinued.

- When LFTs return to normal, an Early Termination (ET) Visit should be conducted to conclude their participation in the study.

Table 1.3-2: Schedule of Activities, Extension Part

Period	Treatment Period (14 months)															Follow-up Period (3 months)			
	Rollover Period (2 months) ⁷	Open-Label Treatment Period (12 months)																	
Visit Name	Rollover V13 ¹	Baseline V14 ⁷	V15	V16	V17	V18	V19, 20	V21	V22	V23	V24	V25	V26	V27	EOT V28 ¹⁰	Call ⁸ V29	Follow-up ⁹ V30 ¹⁰	UNS	ET ¹⁰
Time of Visit	W24	W32	W33	W34	W35	W36	W37, 38	W40	W42	W44	W48	W52	W56	W68	W80	W84	W92		
Visit Window	±3d	±3d	±1d	±1d	±1d	±1d	±1d	±3d	±3d	±3d	±3d	±3d	±7d	±7d	±7d	±3d	-7d onward		
██████████	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█		█	█	█
Placebo Group	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Active Group	X	X						X			X		X	X	X	X	X	X	X
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Concomitant Treatments	Y	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Intervention Administration	Oral dosing once daily (QD)																		
██████████ ██████████ ONO-2808 ³		X ³																	
Adverse Events	Y	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs, Weight	Y	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Orthostatic Blood Pressure	Y	X						X			X		X	X	X		X	X	X
Full Physical, and Neurological Exam	Y	X						X			X		X	X	X		X		X
Brief Physical Exam			X	X	X	X	X		X	X		X						X	
12-Lead ECG	Y	X	X	X		X		X		X	X	X	X	X	X		X		X
Chemistry Panel Including Kidney, LFTs, and Coagulation ⁴	Y	X	X	X ⁴	X ⁴	X	X ⁴	X	X ⁴	X	X	X	X	X	X		X	X ⁴	X
Hematology (CBC with Differential)	Y	X	X			X		X		X	X		X	X	X		X	X	X
Urinalysis ⁵	Y	X	X			X		X		X	X		X	X	X		X	X	X
Pregnancy Test (Urinary)	X	X						X			X		X	X	X		X		X
██████████	Y	X									X				X				X
UMSARS	Y	X						X			X		X	X	X				X

Period	Treatment Period (14 months)															Follow-up Period (3 months)			
	Rollover Period (2 months) ⁷	Open-Label Treatment Period (12 months)																	
Visit Name	Rollover V13 ¹	Baseline V14 ⁷	V15	V16	V17	V18	V19, 20	V21	V22	V23	V24	V25	V26	V27	EOT V28 ¹⁰	Call ⁸ V29	Follow-up ⁹ V30 ¹⁰	UNS	ET ¹⁰
Time of Visit	W24	W32	W33	W34	W35	W36	W37, 38	W40	W42	W44	W48	W52	W56	W68	W80	W84	W92		
Visit Window	±3d	±3d	±1d	±1d	±1d	±1d	±1d	±3d	±3d	±3d	±3d	±3d	±3d	±7d	±7d	±3d	-7d onward		
Placebo Group	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Active Group	X	X						X			X		X	X	X	X	X	X	X
	Y	X						X			X		X	X	X				X
	Y	X						X			X		X	X	X				X
	Y	X						X			X		X	X	X				X
	Y	X						X			X		X	X	X				X
	Y	X						X			X		X	X	X				X
C-SSRS	Y	X						X			X		X	X	X		X		X
Brain MRI ⁶	Y										X				X				X
Liver MRI ⁶	Y	As needed if persistent transaminitis is observed																	

Abbreviations: CBC=Complete Blood Count; C-SSRS=Columbia Suicide Severity Rating Scale; d=day(s); ECG=Electrocardiogram; EOT=End of Treatment; ET=Early Termination; [REDACTED]; LFTs=Liver Function Tests; M=Month(s); MRI=Magnetic Resonance Imaging; [REDACTED];

[REDACTED]; UMSARS=Unified Multiple System Atrophy Rating Scale; UNS=Unscheduled Visit; V=Visit; W=Week(s).

1. All procedures occurring at the rollover visit indicated by a "Y" are part of the SoA for the visit of EOT/V13 of the core part of ONO-2808-03 study and are not to be duplicated.

5. Urinalysis includes pH, bilirubin, ketones, nitrites, glucose, leucocytes, protein, urobilinogen, and blood.

6. Brain and Liver MRI scanning can be combined.

7. Rollover period may be extended for participants affected by site setup activities.

8. PI to conduct a call to the participant 4 weeks after end of treatment for a safety check-in ahead of the onsite safety follow-up visit.

9. It is permissible to delay the final Safety Follow-up visit, so the participant stays an active participant in the study, until the new protocol amendment for the Additional Extension is implemented at the site.

10. If IP discontinuation criteria are met due to elevated LFTs:

- An End of Treatment (EOT) Visit should be conducted as soon as possible

- A Safety Follow-up Visit should be conducted 4 or 12 weeks after IP is discontinued. 4 weeks FU will be applied only to cases requiring further long-term follow-up, including potential-DILI cases. For all other cases 12 weeks FU will be applied.

When LFTs return to normal, an Early Termination (ET) Visit should be conducted to conclude their participation in the study.

Table 1.3-3: Schedule of Activities, Additional Extension Part

Period	Treatment Period (Maximum 72 weeks, 18 months)							Follow-up Period (12 weeks, 3 months)		UNS	ET ¹⁰
	Open-Label Treatment Period (Maximum 72 weeks, 18 months)							Call ² AC	Follow-up AF ¹⁰		
Visit Name	Rollover A1 ¹	A2	A3	A4	A5	A6	A7				
Time of Visit	W0	W12	W24	W36	W48	W60	W72	EOT+W4	EOT+W12		
Visit Window		±7d	±7d	±7d	±7d	±7d	±7d	±3d	±7d		
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Concomitant Treatments	Y	X	X	X	X	X	X	X	X	X	X
Study Intervention Administration ^{4,10}	Oral dosing once daily (QD)										
Adverse Events	Y	X	X	X	X	X	X	X	X	X	X
Vital Signs, Weight	Y	X	X	X	X	X	X		X	X	X
Orthostatic Blood Pressure	Y	X	X	X	X	X	X		X	X	X
Full Physical, and Neurological Exam	Y	X	X	X	X	X	X		X		X
Brief Physical Exam										X	
12-Lead ECG	Y	X	X	X	X	X	X		X		X
Chemistry Panel Including Kidney, LFTs, and Coagulation ⁵	Y	X	X	X	X	X	X		X	X ⁴	X
Hematology (CBC with Differential)	Y	X	X	X	X	X	X		X	X	X
Urinalysis ⁶	Y	X	X	X	X	X	X		X	X	X
Pregnancy Test (Urinary)	Y	X	X	X	X	X	X		X		X
UMSARS	Y	X	X	X	X	X	X				X
	Y	X	X	X	X	X	X				X
C-SSRS	Y	X	X	X	X	X	X		X		X
Brain MRI ^{7,8}	Y				X						X ⁹
Liver MRI ⁷	As needed if persistent transaminitis is observed										

Abbreviations: CBC=Complete Blood Count; C-SSRS=Columbia Suicide Severity Rating Scale; d=day(s); ECG=Electrocardiogram; EOT=End of Treatment; ET=Early Termination; LFTs=Liver Function Tests; MRI=Magnetic Resonance Imaging; [REDACTED]; [REDACTED]; UMSARS=Unified Multiple System Atrophy Rating Scale; UNS=Unscheduled Visit; W=Week(s).

1. All procedures occurring at the rollover/A1 visit indicated by a “Y” are part of the SoA for the visit of EOT/V28 of the extension part and are not to be duplicated. If the rollover/A1 visit is conducted separately from EOT/V28, these items indicated by “Y” except Brain MRI must be performed at the rollover/A1 visit. For participants who had already entered the follow-up period, it is permissible to delay the final Safety Follow-up visit/Rollover/A1 visit, so the participant stays an active participant in the study, until the new protocol amendment for the Additional Extension is implemented at the site. Participants with a gap in treatment should be monitored closely after restarting IMP at the A1 visit, utilizing Unscheduled visits or phone call to the participant as needed, at the PI’s discretion.

2. PI to conduct a call to the participant 4 weeks after end of treatment for a safety check-in ahead of the onsite safety follow-up visit.

[REDACTED]

5. At UNS, only LFTs and coagulation are required when criteria are met per the LFT monitoring guidance. Any other tests may be included at the discretion of the PI for UNS only. LFTs include: alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBL), direct bilirubin (DBL), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK); Coagulation panel includes activated partial thromboplastin time (aPTT), and prothrombin time (PT)/international normalized ratio (INR).

6. Urinalysis includes pH, bilirubin, ketones, nitrites, glucose, leucocytes, protein, urobilinogen, and blood.

7. Brain and Liver MRI scanning can be combined.

8. Only volumetric assessments of white and gray matter, and no DTI

9. If Brain MRI is already performed at the A5 visit, it is not necessary to perform it at the ET visit.

10. If IP discontinuation criteria are met due to elevated LFTs:

- An End of Treatment (EOT) Visit should be conducted as soon as possible

- A Safety Follow-up Visit should be conducted 4 or 12 weeks after IP is discontinued. 4 weeks FU will be applied only to cases requiring long-term follow-up, including potential-DILI cases. For all other cases 12 weeks FU will be applied.

- When LFTs return to normal, an Early Termination (ET) Visit should be conducted to conclude their participation in the study

Table 1.3-4: Schedule of Activities (SoA) by Group and Visit, Extension Part

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
Rollover V13	Week 24 (±3d)		• Informed Consent • Inclusion/Exclusion Criteria • Concomitant Treatments (core part) • Adverse Events (core part) • Vital Signs and Weight (core part) • Orthostatic Blood Pressure (core part) • Full Physical Examination (core part) • Neurologic Examination (core part) • 12-lead ECG (core part) • Chemistry Panel (core part) • Hematology (core part) • Urinalysis (core part) • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS (core part) • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS (core part) • Brain MRI (core part) • Liver MRI (core part)	• Informed Consent • Inclusion/Exclusion Criteria • Concomitant Treatments (core part) • Adverse Events (core part) • Vital Signs and Weight (core part) • Orthostatic Blood Pressure (core part) • Full Physical Examination (core part) • Neurologic Examination (core part) • 12-lead ECG (core part) • Chemistry Panel (core part) • Hematology (core part) • Urinalysis (core part) • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS (core part) • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS (core part) • Brain MRI (core part) • Liver MRI (core part)

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
Baseline V14	Week 32 (±3d)		• Inclusion/Exclusion Criteria • Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS	• Inclusion/Exclusion Criteria • Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS
	Day 1		• [REDACTED] ONO-2808	Not required
V15	Week 33 (±1 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis	Not required

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
V16	Week 34 (±1 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • 12-lead ECG • Chemistry Panel (*Only LFTs and Coagulation required at this specified visit)	Not required
V17	Week 35 (±1 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • Chemistry Panel (*Only LFTs and Coagulation required at this specified visit)	Not required
V18	Week 36 (±1 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis	Not required
V19, 20	Week 37, 38 (±1 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • Chemistry Panel (*Only LFTs and Coagulation required at this specified visit)	Not required

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
V21	Week 40 (±3 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS	• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS
V22	Week 42 (±3 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • Chemistry Panel (*Only LFTs and Coagulation required at this specified visit)	Not required
V23	Week 44 (±3 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • Chemistry Panel	Not required

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
V24	Week 48 (±3 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS • Brain MRI	• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS • Brain MRI
V25	Week 52 (±3 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Brief Physical Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis	Not required

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
V26	Week 56 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS	• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
V27	Week 68 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS	• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
EOT V28	Week 80 (±7 day)		- Concomitant Treatments - Adverse Events - Vital Signs and Weight - Orthostatic Blood Pressure - Full Physical Examination - Neurologic Examination 12-lead ECG - Chemistry Panel - Hematology - Urinalysis - Urine Pregnancy Test (WOCBP) - UMSARS - C-SSRS - Brain MRI	- Concomitant Treatments - Adverse Events - Vital Signs and Weight - Orthostatic Blood Pressure - Full Physical Examination - Neurologic Examination 12-lead ECG - Chemistry Panel - Hematology - Urinalysis - Urine Pregnancy Test (WOCBP) - UMSARS - C-SSRS - Brain MRI
Safety Follow-up Call V29	Week 84 (±3 days)		- Concomitant medications - Adverse Events	- Concomitant medications - Adverse Events

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
Safety Follow-up Visit V30	Week 92 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • C-SSRS	• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • C-SSRS
UNS	Unscheduled		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Brief Physical Examination • Chemistry Panel (*Only LFTs and Coagulation required at this specified visit) • Hematology • Urinalysis	• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Brief Physical Examination • Chemistry Panel (*Only LFTs and Coagulation required at this specified visit) • Hematology • Urinalysis

Visit Number	Time Period (window)		Procedures/Assessments to be Performed	
			Placebo Group	Active Group
ET	Early Termination		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS • Brain MRI	• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • [REDACTED] • UMSARS • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • C-SSRS • Brain MRI

Table 1.3-5: Schedule of Activities (SoA) by Group and Visit, Additional Extension Part

Visit Number	Time Period (window)		Procedures/Assessments to be Performed
Rollover A1	Week 0		• Informed Consent • Inclusion/Exclusion Criteria • Concomitant Treatments (extension part) • Adverse Events (extension part) • Vital Signs and Weight (extension part) • Orthostatic Blood Pressure (extension part) • Full Physical Examination (extension part) • Neurologic Examination (extension part) • 12-lead ECG (extension part) • Chemistry Panel (extension part) • Hematology (extension part) • Urinalysis (extension part) • Urine Pregnancy Test (WOCBP, extension part) • UMSARS (extension part) • [REDACTED] • C-SSRS (extension part) • Brain MRI (extension part) * All procedures occurring at the rollover/A1 visit indicated by a “extension part” are part of the SoA for the visit of EOT/V28 of the extension part and are not to be duplicated. If the rollover/A1 visit is conducted separately from EOT/V28, these items indicated by “extension part” except Brain MRI must be performed at the rollover/A1 visit. It is permissible to delay the final Safety Follow-up visit/A1 visit, so the participant stays an active participant in the study, until the new protocol amendment for the Additional Extension is implemented at your site.

Visit Number	Time Period (window)		Procedures/Assessments to be Performed
A2	Week 12 (±7d)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • • C-SSRS
A3	Week 24 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • • C-SSRS

Visit Number	Time Period (window)		Procedures/Assessments to be Performed
A4	Week 36 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • • C-SSRS
A5	Week 48 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • • C-SSRS • Brain MRI (Only volumetric assessments of white and gray matter, and no DTI)

Visit Number	Time Period (window)		Procedures/Assessments to be Performed
A6	Week 60 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • • C-SSRS
A7	Week 72 (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • • C-SSRS
Safety Follow-up Call AC	EOT + 4 Weeks (±3 days)		• Concomitant Treatments • Adverse Events

Visit Number	Time Period (window)		Procedures/Assessments to be Performed
Safety Follow-up Visit AF	EOT + 12 Weeks (±7 day)		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • C-SSRS
UNS	Unscheduled		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Brief Physical Examination • Chemistry Panel (*Only LFTs and Coagulation required at this specified visit) • Hematology • Urinalysis

Visit Number	Time Period (window)		Procedures/Assessments to be Performed
ET	Early Termination		• Concomitant Treatments • Adverse Events • Vital Signs and Weight • Orthostatic Blood Pressure • Full Physical Examination • Neurologic Examination • 12-lead ECG • Chemistry Panel • Hematology • Urinalysis • Urine Pregnancy Test (WOCBP) • UMSARS • • C-SSRS • Brain MRI (Only volumetric assessments of white and gray matter, and no DTI)* * If Brain MRI is already performed at the A5 visit, it is not necessary to perform it at the ET visit.

2 INTRODUCTION

2.1 Study Rationale

Based on its mechanism of action, ONO-2808 has the potential to provide symptomatic improvement and modify disease progression in patients with MSA by promoting remyelination and reducing pathogenic CNS α -synuclein accumulation. This initial study of ONO-2808 in MSA patients will generate data to evaluate the safety, tolerability, PK, PD, and potential efficacy of 3 doses of ONO-2808 compared to placebo.

2.2 Background

MSA is a rare, rapidly progressing, fatal, adult-onset neurodegenerative disorder of the central and autonomic nervous systems that is characterized clinically by a variable combination of parkinsonism, cerebellar impairment, and autonomic and motor dysfunctions.¹ Together with Parkinson's disease and dementia with Lewy bodies (DLB), MSA belongs to the group of α -synucleinopathies which are morphologically characterized by abnormal accumulation of fibrillary α -synuclein.²⁻⁶ Alpha-synuclein inclusions in oligodendroglia are the recognized neuropathologic hallmarks of MSA,⁴ and may represent the primary pathologic event.⁷ More specifically, this abnormal accumulation of hyperphosphorylated α -synuclein leads to degeneration of oligodendrocytes, loss of myelin, and microglia activation, resulting in oxidative stress and inflammatory reactions. All these events culminate in the degeneration and death of multiple neuronal pathways over the course of the disease, causing a multifaceted clinical picture.⁸⁻¹⁰ Depending on the predominant clinical phenotype, the disease is sub-classified into a parkinsonian variant (MSA-P) associated with striatonigral degeneration, a cerebellar variant (MSA-C) with olivopontocerebellar atrophy and predominant cerebellar features, and a combination of both forms, referred to as "mixed" MSA.^{9,10} The underlying molecular mechanisms are poorly understood, but converging evidence suggests that a "prion-like" spreading of misfolded α -synuclein is a key event in the pathogenic cascade leading to systemic neurodegeneration.^{7,11-13}

There is a large unmet need for neuroprotective strategies in MSA due to its rapid progression to a fatal outcome, and for which there are currently no disease-modifying agents or treatment options. The purpose of this study is to evaluate the safety and effectiveness of ONO-2808 in patients with MSA-C and MSA-P.

ONO-2808 is a novel, oral, small molecule S1PR5 agonist. Sphingosine-1-phosphate (S1P) is a simple membrane-derived lysophospholipid with regulatory roles in almost all facets of mammalian biology.¹⁴ The S1PR5 receptor shows tissue distribution restricted to brain and subsets of immune cells in several tissues, including skin, spleen, and other lymphoid organs.^{15,16} S1PR5 plays an important role in neuronal differentiation and synaptic transmission in neuronal-glial connections and myelin stability.¹⁷ Approximately 35% of plasma S1P is bound to albumin and 65% to Apolipoprotein M (ApoM). ApoM is found on a small percentage (5%) of high density lipoprotein (HDL) particles.¹⁸ Dysregulation of myelin lipids (including sphingolipids) is implicated in the pathogenesis of MSA.

Clinical data for ONO-2808 are available from 2 completed First-in-Human (FIH) studies; ONO-2808-01 and ONO-2808-02 studied healthy adult non-Japanese and Japanese volunteers, respectively.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ONO-2808 is provided in the IB.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ONO-2808 may be found in the IB, development safety update report (DSUR), summary of product characteristics. The potential risks associated with study intervention, additional risks associated with the disease (e.g., orthostatic hypotension) and study procedures are described in the participant informed consent form (ICF).

2.3.1 Risk Assessment

Currently, the risk for hepatotoxicity from ONO-2808 is not fully characterized, and with cumulative ONO-2808 dosing for 6 months, there is a possibility that DILI may occur, even at lower doses. Therefore, ongoing monitoring for hepatotoxicity is needed when subjects are dosed with ONO-2808 during the clinical trial. A thorough description of risks related to the study intervention can be found in the IB.

2.3.2 Benefit Assessment

MSA is a progressive neurodegenerative disorder of the central and autonomic nervous systems, leading to the deterioration of autonomic, motor, and cognitive functions. The study treatment has the potential to benefit study participants receiving the investigational intervention. Although treatment with ONO-2808 has the potential to provide clinical benefit, as this is the initial study in MSA patients, any potential benefit is not yet known.

Benefit considerations may include:

- Potential benefit of receiving investigational intervention during study duration that may have clinical utility
- Contributing to the process of developing new therapies in an area of unmet need

- Additional assessments will be performed to assess the participant's disease that are not part of routine standard of care (e.g., physical and neurological exams, ECG, MRI, and labs)

2.3.3 Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with ONO-2808 are justified by the anticipated benefits that may be afforded to participants with MSA.

3 OBJECTIVES AND ENDPOINTS

The following objectives and endpoints are applicable to the core, the extension, and the additional extension parts of the study, unless indicated.

Objectives	Endpoints
Primary Objective	Primary Endpoint
To evaluate the safety and tolerability of multiple oral doses of ONO-2808 in patients with MSA	- Incidence or change from the baseline in the following assessments: - Incidence and severity of adverse events (AEs) - Vital signs (blood pressure, pulse rate, temperature, respiratory rate) 12-lead electrocardiograms (ECGs); parameters such as, but not limited to, heart rate, RR, PR, QRS, QT, and corrected QT intervals (QTcF) - Clinically-significant abnormal physical examination findings - Clinically-significant laboratory abnormalities (hematology, clinical chemistry, and urinalysis), including survey of drug-induced liver abnormalities - Clinically-abnormal findings in Columbia Suicide Severity Rating Scale (C-SSRS)
Secondary Objectives	Secondary Endpoints
To evaluate the pharmacokinetics (PK) of multiple oral doses of ONO-2808 in patients with MSA	Plasma concentration of ONO-2808 (core part only)
Exploratory	Exploratory Endpoints
To evaluate performance of clinical outcome assessments (COA) in patients with MSA taking multiple doses of ONO-2808	- Change from baseline in the following assessments: - Unified Multiple System Atrophy Rating Scale (UMSARS) 

	■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED]
• [REDACTED]	• [REDACTED] ■ [REDACTED] ■ [REDACTED]
• To evaluate performance of imaging biomarkers in patients with MSA taking multiple doses of ONO-2808	• Imaging parameters may include, but are not limited to: ○ Magnetic resonance imaging (MRI) volumetric assessments of white and gray matter ○ Diffusion tensor imaging (DTI) for white matter abnormalities (core part and extension part only)

4 STUDY DESIGN

4.1 Overall Design

The purpose of this study is to evaluate the safety, tolerability, PK, PD, and potential efficacy of multiple doses of ONO-2808 in patients with MSA.

ONO-2808 is a novel, oral, small molecule sphingosine-1-phosphate receptor-5 (S1PR5) agonist that is being developed for the treatment of MSA. Based on its mechanism of action, ONO-2808 has the potential to provide symptomatic improvement and modify disease progression in patients with MSA by promoting remyelination and reducing pathogenic CNS α -synuclein accumulation.

The results from all parts of this study will also inform the identification of the primary endpoint, sample size, ONO-2808 dose, and design of future clinical studies.

SOC treatments for MSA consistent with local medical practice will be available to all participants during the entire study.

Core Part:

Potential participants will undergo a screening period of up to 6 weeks. Eligible participants 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 participants, followed by a 4-week follow-up period after treatment discontinuation. Participants who complete Week 24 visit in the core part of the study, will rollover to the extension part of the study. Participants who discontinue from the core part of the study or who opt to not continue into the extension part, will complete a 4-week safety follow-up period.

[REDACTED]

After the completion of treatment, participants who continue to meet the relevant inclusion/exclusion criteria and are willing to continue dosing will rollover into the extension part.

Extension Part and Additional Extension Part:

The purpose of the extension part is to evaluate the long-term safety, tolerability, PD, and potential efficacy of multiple doses of ONO-2808 in patients with MSA, continued from ONO-2808-03 study (core part). This extension part will remain blinded during Rollover period, and after that, will be transitioned to open-labeled treatment period.

Eligible participants will continue to receive one of 3 dose levels [REDACTED] of ONO-2808 or a placebo control, as assigned in the core part, for the Rollover period for 8 weeks.

At Visit 14 (week 32), placebo participants (placebo group) will [REDACTED] ONO-2808 for treatment period. Participants on other ONO-2808 doses (active groups) will continue their same ONO-2808 dose for the entirety of the treatment period. ONO-2808 will be administered orally once daily (QD) for treatment period (48 weeks), followed by a 12-week Follow-up period after treatment discontinuation. [REDACTED]

Participants who complete EOT/V28 in the extension part above will be eligible to rollover into an additional extension part. Participants who rollover into this additional extension part will continue the same dose assignment from the extension part. The treatment duration in this additional extension part will vary by participant and is expected to be up to approximately 48 to 72 weeks, depending on the timing of rollover [REDACTED]. All participants will receive study treatment orally once daily (QD) and will be followed up for 12 weeks (follow-up period) after treatment discontinuation. [REDACTED]

Core, Extension, and Additional Extension Parts:

In all parts of the study, liver function will be specifically examined, in response to a limited number of transaminitis events seen during Phase 1 studies of ONO-2808 in healthy volunteers. Participants and caregivers will be instructed to report any DILI-related signs and symptoms, such as abdominal pain, nausea, vomiting, loss of appetite, dark urine, yellow eyes, or pruritis, or persistent fatigue, during treatment administration and during the follow-up period. Participants should seek immediate medical attention if any DILI-related signs and symptoms occur in trial participants either during the treatment period or up to 60 days after receiving the last dose of investigational agent.

4.2 Scientific Rationale for Study Design

Based on its mechanism of action, ONO-2808 has the potential to provide symptomatic improvement and modify disease progression in patients with MSA by promoting remyelination

and reducing pathogenic CNS α -synuclein accumulation. This initial study of ONO-2808 in MSA patients will generate data to evaluate the safety, tolerability, PK, PD, and potential efficacy of 3 doses of ONO-2808 compared to placebo. The extension part will generate data to evaluate the long-term safety, tolerability, PD, and potential efficacy of participants in MSA patients. Participants will receive [REDACTED] or matching placebo for 24 weeks during the core part. Those receiving an active dose of ONO-2808 will continue to receive the same dose for 56 weeks in the extension part. Placebo to experimental participants will receive placebo during the rollover period (8 weeks) and then [REDACTED] ONO-2808 QD for the remaining 48 weeks. This will allow for a total of 80 weeks of treatment between the core and extension parts of ONO-2808-03, providing extended access to the experimental treatment, ONO-2808, and long-term safety examinations.

4.2.1 Transaminitis/Hepatotoxicity of ONO-2808 Observed in Phase 1 Studies

ONO-2808 has been investigated in two Phase 1 studies in non-Japanese (Study ONO-2808-01) and Japanese (Study ONO-2808-02) healthy adult volunteers. The ONO-2808-01 study was a randomized, double-blind, placebo-controlled, single center study to assess the safety, tolerability and pharmacokinetics of single and multiple oral doses of ONO-2808 in non-Japanese healthy subjects. [REDACTED]

[REDACTED] The ONO-2808-02 study was a randomized, double-blind, placebo-controlled, single center study to assess the safety, tolerability and pharmacokinetics of single and multiple oral doses of ONO-2808 in Japanese healthy subjects. [REDACTED]

[REDACTED] Therefore, a double-blind, parallel-group, placebo-controlled 6-month design with ONO-2808 dosages [REDACTED] proposed for this study is predicted to have a low probability of self-limiting transaminitis in MSA patients with no pre-existing liver diseases or cirrhosis.

4.2.2 Ongoing Monitoring for Hepatotoxicity

[REDACTED]

Ongoing monitoring for hepatotoxicity is therefore needed when subjects are dosed with ONO-2808 during the proposed trial. Frequent monitoring of liver function parameters in all participants is planned throughout this study (i.e., liver function test [LFT] at baseline, weekly for the first 6 weeks of dosing, bi-weekly over the next 6 weeks, and monthly thereafter.) If LFT results are above upper limit of normal and trending up, monitor LFT weekly; then at least bi-weekly when trending down until resolution. The LFT panel will include alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBL), direct bilirubin (DBL), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) at baseline and at follow-up. In addition, blood coagulation monitoring will include activated partial thromboplastic time (aPTT), prothrombin time (PT), and the international normalized ratio (INR).

DILI-related individual stopping criteria and trial stopping criteria are proposed for the study following the FDA Guidance for Industry on DILI.¹⁹

4.2.3 Monitoring of Participants with Elevated Liver Function Tests (LFTs)

Additional monitoring of LFTs will be initiated upon detection and confirmation of early signals of possible DILI (ALT or AST $>3 \times$ ULN). Guidance on monitoring of participants with elevated LFTs is provided in [Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments](#).

[REDACTED]

All trial participants and their caregivers will be educated about signs and symptoms of liver injury, such as abdominal pain, nausea, vomiting, loss of appetite, dark urine, yellow eyes, pruritis, or persistent fatigue. Should these symptoms occur in trial subjects either during the clinical trial or up to 60 days after receiving the last dose of the investigational agent, they should seek immediate medical attention and report to the Investigator as soon as possible.

4.2.4 Parallel-Group Study Design

4.2.5 Patient Input to Study Design

The Sponsor has conducted several consultation meetings with patients living with MSA, their caregivers, specialist nurses and representatives from MSA patient advocacy organizations. The Sponsor team learned in detail the patient journey from their own perspectives. The study design, patient characteristics, and study procedure were discussed in detail.

The overall feedback from the patients and their caregivers was positive. Panel members reported that the study design was very patient centric, and there were no concerns related to the study scheduled activities.

MSA patients realize they may not be directly benefiting from this study, but it will help future generations of MSA patients.

4.3 Justification for Dose

Careful monitoring of liver function parameters and a detailed guidance on monitoring of participants with elevated LFTs is considered necessary in all dose cohorts in this study.

4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit and the last scheduled procedure shown in the SoA.

The date of completion of the participant is defined as the date of the last visit of the last scheduled procedure for the study. The date of completion or discontinuation is to be recorded in the electronic Case Report Form (eCRF).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

5.1.1 Inclusion Criteria for the Core Part

Participants are eligible to be included in this core part only if all of the following criteria apply:

Age
1. Participant must be 30 to 80 years of age inclusive, at the time of signing the informed consent.
Type of Participant and Disease Characteristics
2. Female or male patients with a diagnosis of clinically-established or clinically-probable MSA according to the novel Movement Disorder Society (MDS) criteria for MSA diagnosis (2022) ²⁰ , including patients with MSA of either subtype (MSA-P or MSA-C). 3. Patients at the early stages of the disease, defined as a maximum of 5 years since the onset of one of the following symptoms associated with MSA: • Parkinsonism • Ataxia • Orthostatic hypotension and/or urinary dysfunction 4. Patients with an anticipated survival of at least 3 years in the opinion of the Investigator. 5. Patients who are able to ambulate without the assistance of another person, defined as the ability to take at least 10 steps and then to turn around and walk at least another 10 steps. Use of assistive devices (e.g., walker or cane) is allowed. 6. Ability to swallow oral medication and be willing to adhere to the study intervention regimen.
Sex and Contraceptive/Barrier Requirements
7. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner, as recommended by local guidelines relating to contraception during clinical trials.
Informed Consent
8. Participants must provide informed consent directly (or through their legal authorized representatives) after reading the information and consent form and after having the opportunity to discuss the study with the Investigator or designee. While participants who

require a legally authorized representative to provide consent are eligible in the main study, these participants will not be eligible for the optional biomarker sub-study.
Other Inclusion Criteria
9. Patients who agree to comply with the restrictions and requirements of the study. 10. For menopausal women, Follicle-Stimulating Hormone (FSH) test confirmation is required. 11. Patients vaccinated for SARS-CoV-2 prior to Screening or history of SARS-CoV-2 infection documented by the PI. 12. Participants must be able to understand the nature of the study, the risks, discomforts, and inconveniences involved in the study, to communicate satisfactorily with the Investigator, and to participate and comply with the requirements of the entire study.

5.1.2 Inclusion Criteria for the Extension Part

Participants are eligible to be included in this extension part only if all of the following criteria apply:

Type of Participant and Disease Characteristics
1. Participants must be completers of the core part of ONO-2808-03 study thus meeting all MSA diagnostic criteria outlined in that protocol. 2. Ability to swallow oral medication and be willing to adhere to the study intervention regimen.
Sex and Contraceptive/Barrier Requirements
3. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner, as recommended by local guidelines relating to contraception during clinical trials.
Informed Consent
4. Participants must provide informed consent directly (or through their legal authorized representatives) after reading the information and consent form and after having the opportunity to discuss the study with the Investigator or designee.
Other Inclusion Criteria
5. Participants who agree to comply with the restrictions and requirements of the study. 6. For menopausal women, Follicle-Stimulating Hormone (FSH) test confirmation if applicable.

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|--|
| <p>7. Participants must be able to understand the nature of the study, the risks, discomforts, and inconveniences involved in the study, to communicate satisfactorily with the Investigator, and to participate and comply with the requirements of the entire study.</p> |
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5.1.3 Inclusion Criteria for the Additional Extension Part

Participants are eligible to be included in this additional extension part only if all of the following criteria apply:

Type of Participant and Disease Characteristics
8. Participants must be completers of the open-label extension part of ONO-2808-03 study thus meeting all MSA diagnostic criteria outlined in that protocol. 9. Ability to swallow oral medication and be willing to adhere to the study intervention regimen.
Sex and Contraceptive/Barrier Requirements
10. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner, as recommended by local guidelines relating to contraception during clinical trials.
Informed Consent
11. Participants must provide informed consent directly (or through their legal authorized representatives) after reading the information and consent form and after having the opportunity to discuss the study with the Investigator or designee.
Other Inclusion Criteria
12. Participants who agree to comply with the restrictions and requirements of the study. 13. For menopausal women, Follicle-Stimulating Hormone (FSH) test confirmation if applicable. 14. Participants must be able to understand the nature of the study, the risks, discomforts, and inconveniences involved in the study, to communicate satisfactorily with the Investigator, and to participate and comply with the requirements of the entire study.

5.2 Exclusion Criteria

5.2.1 Exclusion Criteria for the Core Part

Participants are excluded from the core part if any of the following criteria apply:

Medical Conditions

1. Pregnant or lactating females. 2. Patients with a clinically-significant or unstable medical or surgical condition other than MSA that, in the opinion of the Investigator, might preclude safe completion of the study or might affect the results of the study (e.g., pulmonary, cardiovascular [including bradyarrhythmia], macular edema, and significant renal or hepatic dysfunction).** 3. Neurological diseases/disorders other than MSA, such as Parkinson's disease, dementia with Lewy bodies, essential tremor, progressive supranuclear palsy, spinocerebellar ataxia, spastic paraparesis, corticobasal degeneration, or vascular, normal pressure hydrocephalus, pharmacological, or post-encephalitic parkinsonism. 4. Patients with documented liver diseases or cirrhosis. 5. Positive results at Screening for active viral infections that include positive human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) and hepatitis B core antibody, and hepatitis C virus (HCV). 6. Patients with suicide ideation according to the Investigator's clinical judgment per the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening or who have made a suicide attempt in the 6 months before Screening.
Prior/Concomitant Therapy
7. For patients receiving treatment (including chronic medications, and herbal or dietary supplements) for symptoms associated with MSA, the dosage must have been stable for at least 60 days prior to randomization, based on the judgment of the Investigator; any medication is expected to remain stable during the study period. 8. History of electroconvulsive therapy and/or history of deep brain stimulation therapy. 9. Patients taking drugs prohibited by the study protocol, as outlined in Section 6.9.1 Prohibited Therapies. 10. Regular use of neuroleptics within 6 months prior to the initial evaluation. Occasional use of a neuroleptic as an anti-emetic in the past is allowed, providing not more than 3 doses were taken within the previous 12 months.
Prior/Concurrent Clinical Study Experience
11. Patients who have taken any investigational products within 14 days or five half-lives (whichever is longer) of first dosing and throughout the study.
Diagnostic Assessments
12.  13. Clinically-significant ECG abnormality as judged by the Investigator.

14. Confirmed absolute QTcF > 450 msec for males and > 470 msec for females and/or an increase of > 60 msec on repeated ECGs performed at least 2 minutes apart. 15. Patients with a contraindication for MRI scanning, including those with an MRI-incompatible pacemaker.
Other Exclusion Criteria
16. Women of childbearing potential (WOCBP) who do not practice an acceptable method of birth control, as recommended by local guidelines [acceptable methods of birth control in this study are: Surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy, a double-protection method (condom or diaphragm with spermicide). 17. Patients consuming more than moderate levels of alcohol, defined as more than 1 standard drink per day for women and more than 2 standard drinks per day for men. 18. [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
** Other clinically-significant or unstable medical or surgical conditions may include: • Severe uncontrolled congestive heart failure • Recent (< 6 months) myocardial infarct • Severe uncontrolled cardiopulmonary disease

- Severe, uncontrolled hypertension (sustained systolic blood pressure above 200 mmHg in any position)
- Thrombocytopenia ($< 50 \times 10^9/L$)
- Severe anemia (< 8 g/dL)
- Immunocompromised state
- Liver (ALT, AST $> ULN$; TBL $> ULN$) or kidney disease (creatinine > 1.5 mg/dL, creatinine clearance [using Cockcroft-Gault equation] < 60 mL/min, or proteinuria > 20 mg/dL)
- Uncontrolled diabetes mellitus (HbA1c $> 10\%$)
- Alcoholism
- Amyloidosis
- Uncontrolled hypothyroidism
- Sympathectomy
- Unstable peripheral neuropathies
- Concurrent infections
- Severe orthopedic problems that compromise mobility and activity of daily living
- Recent (< 6 months) cerebrovascular accidents
- Neurotoxin or neuroactive drug exposure

5.2.2 Exclusion Criteria for the Extension Part

Participants are excluded from this extension part if any of the following criteria apply:

Medical Conditions
1. Pregnant or lactating females. 2. Participants with suicide ideation according to the Investigator's clinical judgment per the Columbia Suicide Severity Rating Scale (C-SSRS) at the Rollover visit.
Concomitant Therapy
3. Participants taking drugs prohibited by the study protocol, as outlined in Section 6.9.1 Prohibited Therapies.
Concurrent Clinical Study Experience
4. Participants may not concurrently enroll in another clinical study.

Other Exclusion Criteria
5. Women of childbearing potential (WOCBP) who do not practice an acceptable method of birth control, as recommended by local guidelines [acceptable methods of birth control in this study are: Surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy, a double-protection method (condom or diaphragm with spermicide)]. 6. Participants consuming more than moderate levels of alcohol, defined as more than 1 standard drink per day for women and more than 2 standard drinks per day for men.

5.2.3 Exclusion Criteria for the Additional Extension Part

Participants are excluded from this additional extension part if any of the following criteria apply:

Medical Conditions
1. Pregnant or lactating females. 2. Participants with suicide ideation according to the Investigator's clinical judgment per the Columbia Suicide Severity Rating Scale (C-SSRS) at the Rollover/A1 visit.
Concomitant Therapy
3. Participants taking drugs prohibited by the study protocol, as outlined in Section 6.9.1 Prohibited Therapies.
Concurrent Clinical Study Experience
4. Participants may not concurrently enroll in another clinical study.
Other Exclusion Criteria
5. Women of childbearing potential (WOCBP) who do not practice an acceptable method of birth control, as recommended by local guidelines [acceptable methods of birth control in this study are: Surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy, a double-protection method (condom or diaphragm with spermicide)]. 6. Participants consuming more than moderate levels of alcohol, defined as more than 1 standard drink per day for women and more than 2 standard drinks per day for men. 7. Participants who have completed the follow-up period and concluded participation in the study entirely.

5.3 Lifestyle Considerations

MSA is a neurodegenerative disorder of the central and autonomic nervous systems, leading to the deterioration of autonomic and cognitive function. To prolong and maintain function as long as possible, the participant may continue to receive additional treatments such as physiotherapy, occupational therapy and speech therapy but no new start of this type of therapy is allowed within the study, unless necessary to treat severe hypotension of the participants.

5.3.1 Meals and Dietary Restrictions

There are no meal or dietary restrictions in this study.

5.3.2 Caffeine, Alcohol, and Tobacco

Participant is not allowed to consume more than moderate levels of alcohol (defined as more than 1 standard drink per day for women and more than 2 standard drinks per day for men). There is no specific restriction on caffeine or tobacco use in this study.

5.3.3 Activity

There is no limitation on physical activity during this study.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. At a minimum, the screen failure information to be recorded in the eCRF includes the participant identification number, date of consent, date of withdrawal, age, sex, race, ethnicity, any AEs, and reason for withdrawal (for participants who failed to meet any inclusion criterion or met exclusion criterion, the inclusion/exclusion criterion should be specified).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A new subject ID number will be assigned for participants who are rescreened. The eCRF will capture the participant's original screening number and the rescreen number, both of which will be provided in a listing in the Clinical Study Report.

5.5 Criteria for Temporarily Delaying

This section is not applicable.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study interventions are all pre-specified, investigational medicinal products intended to be administered to the participants during the study.

6.1 Study Intervention(s) Administered

Table 6.1-1: Study Intervention(s) Administered

Intervention Label	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3	Treatment Arm 4
Intervention Name	[REDACTED]	[REDACTED]	[REDACTED]	Placebo
Intervention Description	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Type	Drug	Drug	Drug	Drug
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Unit Dose Strength(s)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dosage Level(s)	[REDACTED]	[REDACTED]	[REDACTED]	0 mg
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Placebo
IMP and AxMP	IMP	IMP	IMP	Placebo

Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Table 6.1-2: Study Arm(s) for the Core Part

Arm Title	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3	Treatment Arm 4
Arm Type	Experimental	Experimental	Experimental	Placebo
Arm Description	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Associated Intervention Labels	[REDACTED]	[REDACTED]	[REDACTED]	Placebo

Table 6.1-3: Study Arm(s) for the Extension Part, Rollover Period

Arm Title	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3	Treatment Arm 4
Arm Type	Experimental	Experimental	Experimental	Placebo

Arm Description				
Associated Intervention Labels				Placebo

Table 6.1-4: Study Arm(s) for the Extension Part, Open-Label Treatment Period

Arm Title	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3	Treatment Arm 4
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description				
Associated Intervention Labels				

Table 6.1-5: Study Arm(s) for the Additional Extension Part, Open-Label Treatment Period

Arm Title	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3	Treatment Arm 4
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description				
Associated Intervention Labels				

6.1.1 Dosage and Duration of Treatment

This is the first study of ONO-2808 in patients with MSA. Potential participants will undergo a screening period of up to 6 weeks. Eligible participants will be assigned to receive 1 of 3 dose levels [REDACTED] ONO-2808 or a placebo control. ONO-2808 or placebo will be administered orally once daily (QD) for 24 weeks. After the completion of treatment in the core part, participants may continue treatment in the extension part. Participants who do not continue in the extension part will enter a follow-up period for 4 weeks after treatment discontinuation.

Completers of the core part who wish to continue treatment will rollover to the extension part at the week 24 visit. All participants who are on active doses [REDACTED] in the core part will continue taking the same dose through the entire extension part. All placebo participants will continue on the placebo (administered once daily (QD)) for 8 weeks during the rollover period and then [REDACTED] for the remainder of the study (48 weeks). The

total treatment period for the extension part is 14 months. After the completion of treatment in the extension part, participants may continue treatment in the additional extension part.

Participants who complete EOT/V28 (week 80 visit) in the extension part above will be eligible to rollover into an additional extension part. Participants who rollover into this additional extension part will continue the same dose assignment from the extension part. The treatment duration in this additional extension part will vary by participant and is expected to be up to approximately 48 to 72 weeks, depending on the timing of rollover [REDACTED]. All participants will receive study treatment orally once daily (QD).

6.1.2 Discontinuation for Supply of Study Intervention

The study intervention may be supplied to participants by the Sponsor unless participants meet requirements in [Section 7.1 Discontinuation of Study Intervention](#). The Sponsor will stop the supply of the study intervention if any of the following occurs:

1. The Sponsor withdraws the marketing application for this indication, or
2. The study is terminated.

6.2 Preparation, Handling, Storage, and Accountability

1. The Investigator or designee must confirm that appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.
4. The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition of records).
5. Refer to the current version of the IB and/or instructions for handling of study intervention management for storage, handling, dispensing, and infusion information.
6. Further guidance and information for the final collection/disposition of unused study interventions are provided in the pharmacy manual.

6.3 Assignment to Study Intervention

Core Part:

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

[REDACTED] Randomization will be performed using an interactive

voice/web response system (IVRS/IWRS) or a suitable independent randomization provider.

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

All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Extension Part and Additional Extension Part:

Participants will transition from the Core part of the ONO-2808-03 study at the week 24 visit to the extension part of the 2808-03 study. All participants who are on active doses [REDACTED] in the core part will continue taking the same dose through the entire extension part. All placebo participants will continue on the placebo (administered once daily (QD)) for 8 weeks during the rollover period and then [REDACTED] for the remainder of the study (48 weeks). The total treatment period for the extension part is 14 months.

In the additional extension part, participants will continue the same dose assignment from the extension part. The treatment duration in this additional extension part will vary by participant and is expected to be up to approximately 48 to 72 weeks, depending on the timing of rollover [REDACTED]. All participants will receive study treatment orally once daily (QD).

Core, Extension, and Additional Extension Parts:

Study intervention will be dispensed at the study visits as summarized in the SoA.

Returned study intervention should not be re-dispensed to the participants.

6.4 Blinding

This is a randomized, double-blind followed by open-label, parallel-group, placebo-controlled Phase 2 study.

The treatment for each individual participant will remain blinded during the 6-month core part and the 2-month rollover period of the study, until the clinical report forms of the individual participant from the core part of the study are frozen during the 2-month rollover period. The treatment of each individual participant will be unblinded at Visit 14 at the time the participant enters the 12-month open-label treatment period.

6.5 Study Intervention Compliance

Participants will self-administer study intervention(s) at home, and compliance with study intervention will be assessed at each visit. Compliance, and any symptoms experienced at home, will be further assessed by a diary kept by the participant to be returned during the site visits, with documentation in the source documents and relevant form/eCRF. Deviation(s) from the prescribed dosage regimen will be recorded in the eCRF.

A record of the quantity of ONO-2808 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

6.6 Dose Modification

Dose modifications for participants are not allowed during the study; however, drug interruptions will be allowed based on the judgment of the Investigator in conjunction with the Sponsor. If a participant experiences AEs that meet the individual discontinuation criteria during treatment with ONO-2808 as described in [Section 7.1 Discontinuation of Study Intervention](#), the participant will be discontinued from further treatment, but will be followed for safety outcomes.

6.6.1 Dose Criteria

Core Part:

Eligible participants will be assigned to receive one of 3 dose levels of ONO-2808 or placebo, which will be administered orally once daily (QD) for 24 weeks.

Extension Part and Additional Extension Part:

Eligible participants will continue their assigned dose from the core part of the study, one of 3 dose levels of ONO-2808, which will be administered orally once daily (QD) for 14 months. Placebo participants will continue on placebo for 8 weeks and then will [REDACTED] ONO-2808 for the remaining 48 weeks.

In the additional extension part, participants will continue the same dose assignment from the extension part. The treatment duration in this additional extension part will vary by participant and is expected to be up to approximately 48 to 72 weeks, depending on the timing of rollover [REDACTED]. All participants will receive study treatment orally once daily (QD).

6.6.2 Dose Delay Criteria for Study Intervention

If a patient experiences a non-transaminitis or non-DILI-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. If a patient experiences a transaminitis- or DILI-related AE, please refer to [Appendix 3: AEs and SAEs: Procedures for Recording, Evaluating, Follow-up, and Reporting](#) for guidance on monitoring of participants with elevated LFTs.

6.6.3 Criteria to Resume Study Intervention

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

6.6.4 Re-treatment Criteria

While there are no re-treatment criteria for participants, after the completion of treatment, participants who continue to meet the relevant inclusion/exclusion criteria and are willing to continue dosing will rollover to the extension part.

6.7 Continued Access to Study Intervention After the End of the Study

There is currently no continued access to study intervention following this study.

6.8 Treatment of Overdose

There are currently no criteria for treatment of overdose. Blinded review of the exposure data will be conducted on an ongoing basis.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment, or receives during the study, must be recorded in the eCRF along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The medical monitor/Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Prohibited Therapies

For patients receiving treatment (including chronic medications, and dietary or herbal supplements) for symptoms associated with MSA, the dosage must have been stable for at least 60 days prior to randomization, based on the judgment of the Investigator; any medication is expected to remain stable during the study period.

Regular use of neuroleptics within 6 months prior to the initial evaluation is prohibited. Occasional use of a neuroleptic as an anti-emetic in the past is allowed, providing not more than 3 doses were taken within the previous 12 months.

6.9.2 Permitted Therapies

The dose for permitted medications which are being taken at baseline should remain stable to the extent possible during the study. As needed (PRN) dosing or any dose alternations must be documented in the participant's medical record and in the eCRF.

Permitted medications prescribed to MSA participants may include, but are not limited to, the following:

- Parkinsonism-related therapy (e.g., carbidopa/levodopa)
- Other parkinsonian therapies and supplements
- Blood pressure-augmenting medication/Orthostatic hypotension medications
- Antihypertensive medications
- Supplementary agents
- Post-prandial hypotension medications
- Antidepressant or anti-anxiety medications
- Sleep disorder medications
- Erectile dysfunction medications
- Urinary dysfunction medications
- Constipation medications
- Botulinum toxin

MSA participants will continue to regularly use their pre-existing medications and treatments, which are part of the medical SOC treatment, including physical, occupational, and speech therapy, that are helpful for the supportive care of participants with MSA.

6.9.3 Treatments Requiring Caution or Action

Drugs considered to have significant drug-drug interaction (DDI), such as P-glycoprotein (P-gp) inhibitors, should be administered with caution if they are part of the patient's SOC treatment.

Use of alpha- and beta-adrenergic receptor antagonists, or other medications that affect autonomic function evaluation, should be discussed on an individual basis with the Sponsor.

6.9.4 Rescue Medicine

Currently there are no approved treatments for MSA, and therefore no rescue medication is recommended. Appropriate supportive care and/or pharmacologic intervention will be provided by the primary physician and/or Investigator, as warranted by the participant's condition, if necessary.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in [Appendix 1: Regulatory, Ethical, and Study Oversight Considerations](#).

7.1 Discontinuation of Study Intervention

This study will proceed as planned, unless temporarily halted or stopped by the Sponsor of its own opinion or on the recommendation of the IDMC, IRB/IEC, or competent health authority, after consideration of all available safety data, and with reference to the stopping rules.

7.1.1 Reason for Discontinuation

In rare instances, such as those listed below, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for safety outcomes. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

1. Withdrawal by Subject: The participant's request to discontinue study intervention
2. Withdrawal by Parent/Guardian: The designee of participant's request to discontinue study intervention
3. Adverse Event: The Investigator considers that it is difficult to continue study intervention because of non-tolerable AEs, regardless of whether a causal relationship with the study intervention exists
4. Protocol Deviation: A major variation from processes or procedures defined in a protocol (e.g., participant failed to meet the inclusion criteria or met the exclusion criteria, etc.)
5. Progressive Disease: The Investigator considers that it is difficult to continue study intervention because of disease progression (this includes MSA disease progression)
6. Pregnancy: In case of pregnancy (see [Section 8.4.8 Pregnancy](#))
7. Lost to Follow-up: The participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site
8. Death: In case of death
9. Physician Decision: The Investigator considers that it is not appropriate to continue the study intervention for any other reason
10. Non-Compliance with Study Drug: An indication that a participant has not agreed with or followed the instructions related to the study medication
11. Study Terminated by Sponsor: The clinical study is stopped by the Sponsor
12. Discontinuation for Supply of Study Intervention: When the Sponsor determines that the supply of investigational drug will be stopped in accordance with [Section 6.1.2 Discontinuation for Supply of Study Intervention](#)

13. Protocol-Specified Withdrawal Criterion Met: The participant has met one or multiple protocol-specified withdrawal criteria and has been removed from the study

7.1.2 Liver Chemistry Stopping Criteria

For guidance on monitoring of participants with elevated LFTs, refer to [Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments](#).

The potential for liver injury and its signs and symptoms will be outlined in the informed consent document. Investigators and their designees should educate participants and their caregivers about the signs and symptoms of liver injury, such as abdominal pain, nausea, vomiting, loss of appetite, dark urine, yellow eyes, pruritis, or persistent fatigue. Should these symptoms occur in trial participants, either during the clinical trial or up to 60 days after receiving the last dose of the investigational agent, participants should report to the Investigator and seek immediate medical attention.

7.1.3 Discontinuation Criteria for Individual Participant

Participants may discontinue study intervention at any time and without prejudice to their future care. Participants who receive at least one dose and then discontinue study intervention will enter the 4-week or the 3-month safety follow-up period, depending on which part of the study they are in at the time.

As appropriate, after discussion with the Sponsor, the Investigator should consider withdrawal of a subject from treatment if any of the following events are evident at any time during the study:

1. The patient experiences non-tolerable AEs, judged by the Investigator to be related to ONO-2808 or study procedures, or if the Investigator considers it not to be in the best interest of the patient to continue within the study (this includes MSA disease progression)
2. The patient exhibits increased suicidal risk, suicidal ideation or behavior, or attempts suicide
3. Hepatic toxicity (See [Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments](#))
4. Decrease in creatinine clearance (using Cockcroft-Gault equation) to below 60 mL/min or increases in serum creatinine clinically indicative of acute kidney injury
5. Clinically-significant change in clinical biochemistry and hematology parameters considered related to IMP and confirmed by repeat measurement
6. Unacceptable pharmacological effects (suspected to be related to off-target alpha adrenergic receptor antagonism, such as increased HR, BP, low body temperature) observed in any patient, and attributable by the Investigator to dosing of IMP
7. Pregnancy
8. Non-adherence with IMP dosing (including patient no longer able to swallow medication), study procedures, or restrictions which could have significant impact on subject safety or data integrity
9. If the patient no longer meets the diagnostic criteria for clinically-established or clinically -probable MSA-P or MSA-C, in accordance with the novel MDS criteria for MSA

diagnosis 2022²⁰

The Investigator should discuss with the Sponsor a potential for withdrawal prior to withdrawing a participant from treatment, if possible.

Every effort will be made to continue to follow subjects removed from treatment for safety outcomes until the intended completion of the study.

[illegible]

7.1.4 Discontinuation Criteria for Dose Cohort

7.1.5 Discontinuation Criteria for Study

This study will proceed as planned, unless temporarily halted or stopped after consideration of all available safety data by:

1. Sponsor of its own opinion, or
2. Recommendation of the IDMC, or
3. Request from IRB/IEC or regulatory authority.

After consideration of all available safety data and with reference to the stopping rules as defined in the following sections.

7.1.6 QTc Stopping Criteria

If a clinically-significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the Investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically-relevant finding should be reported as an AE.

7.1.7 Temporary Discontinuation

Criteria for temporary discontinuation can be found in [Section 6.6 Dose Modification](#).

7.1.8 Re-challenge

Study intervention re-challenge is not allowed in this study. A discontinuation of the study intervention should be clearly documented and reflected on the Drug Exposure eCRF panel. AE/SAEs will be reported as appropriate.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason)
- A participant may be withdrawn at any time at the discretion of the Investigator for safety reasons
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed
- The participant may be permanently discontinued from the study intervention and the study at that time
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized/enrolled, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

The study schedule, including study assessments and procedures, are summarized in [Section 1.3 Schedule of Activities \(SoA\)](#). Detailed instructions on conduct of study procedures may be outlined further in an investigator site file, separate from this protocol.

Protocol waivers or exemptions are not allowed.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for Screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.1 Administrative Procedures

The study schedule, including study assessments and procedures are summarized in [Section 1.3 Schedule of Activities \(SoA\)](#).

Administrative procedures will include informed consent, inclusion/exclusion criteria, demographics, medical history, MSA medication history, concomitant treatments, AEs, and randomization. The complete informed consent process can be found in [Section 10.1.3 Informed Consent Process](#).

8.2 Clinical Outcomes Assessments

Planned time points for all clinical outcomes assessments are provided in [Section 1.3 Schedule of Activities \(SoA\)](#).

Details of each assessment are available in [Appendix 7: Clinical Outcomes Assessment Descriptions](#).

8.3 Safety Assessments

A complete list of safety assessments can be found in [Section 1.3 Schedule of Activities \(SoA\)](#).

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any clinically significant finding(s) should be recorded in the eCRF as a Current Medical Conditions or an AE.

8.3.2 Height and Body Weight

Height and body weight will be measured and recorded in the eCRF.

8.3.3 Vital Signs

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within a half hour before or after the scheduled blood draw.

Vital signs will be measured after 5 minutes rest and will include body temperature, systolic and diastolic BP, pulse, and respiratory rate.

Blood pressure and pulse measurements will be done using the same method according to local practice.

Core Part: Screening, Baseline, V10, V13, ET

Extension Part: V14, V21, V24, V26, V27, V28, V30, ET

Additional Extension Part: A1 (if needed), A2, A3, A4, A5, A6, A7, AF, ET

Orthostatic blood pressure will be measured after 5 minutes of lying down, after 1 minute of standing, and after 3 minutes of standing. Blood pressure, pulse rate, and associated symptoms should be captured in each instance.²⁴

Body temperature will be measured using the same method according to local practice. The measured values are to be recorded in degrees Fahrenheit and/or Celsius.

Respiratory rate will be measured by counting breaths over a period of 1 minute (breaths/min) after a resting period of at least 5 minutes in resting position.

For vital signs, summary statistics and changes from baseline will be calculated at each time point.

8.3.4 Electrocardiograms

Triplicate 12-Lead ECG(s) will be obtained using an ECG machine that automatically measures RR, PR, QRS, QT, and corrected QT intervals (QTcF), and the data will be recorded in the eCRF. For ECG parameters (e.g., RR interval, QT interval, and QTc), summary statistics and changes from baseline will be calculated at each time point.

Participants should rest in a supine position for at least 5 minutes prior to each ECG assessment.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be completed within 10 minutes, with each tracing taken as closely as possible in succession, but no more than 2 minutes apart.

The ECG will be repeated if the average QTc exceeds 500 msec or >60 msec change from baseline (average of Day 1 pre-dose measurements) or if judged by the Investigator to be clinically appropriate. Additional 12-lead ECGs will be performed if judged by the Investigator or designee to be clinically appropriate.

8.3.5 Clinical Safety Laboratory Tests

- See [Appendix 2: Clinical Laboratory Tests](#) for the list of clinical laboratory tests to be performed and the SoA ([Section 1.3](#)) for the timing and frequency.
- Frequent monitoring of liver function parameters in all participants is also planned throughout this study (i.e., LFT at baseline, weekly for the first 6 weeks of dosing, bi-weekly over the next 6 weeks, and monthly thereafter). The LFT panel includes alanine transaminase (ALT), aspartate transaminase (AST), TBL, DBL, GGT, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) at baseline and at follow-up. In addition, blood coagulation monitoring will include activated partial thromboplastin time (aPTT), prothrombin time (PT), and the international normalized ratio (INR).
- Scheduled laboratory tests will be analyzed at a central laboratory. Unscheduled laboratory tests may be analyzed at a local laboratory, and the local test results should be accompanied by reference range values and units of measure.
- The Investigator must review the laboratory results, document this review, and record any clinically-significant changes occurring during the study as an AE. The laboratory results must be retained with source documents, and the results recorded in the eCRF.
- All laboratory tests with values considered clinically-significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
 - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

- All protocol required laboratory tests, as defined in [Appendix 2: Clinical Laboratory Tests](#), must be conducted in accordance with the laboratory manual and the SoA ([Section 1.3](#)).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.6 Pregnancy Testing

For a participant who is a woman of childbearing potential (WOCBP), a serum or urine beta human chorionic gonadotrophin (β -hCG) pregnancy test will be performed at Screening. Additional pregnancy tests may be performed at the discretion of the Investigator.

The same test method should be used throughout the study period as much as possible.

Results of pregnancy tests are required prior to the start of ONO-2808 dosing. If the results are positive, dosing will not proceed, and the participant will be withdrawn from the study.

8.3.7 Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with ONO-2808 should 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, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated, and consideration given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with ONO-2808 should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of SIB, and to report such symptoms immediately to the study Investigator. The study Investigator will decide if appropriate therapy will be initiated, or if the participant needs to be referred to a psychiatrist.

Baseline assessment of suicidal ideation and behavior/intervention-emergent SIB will be monitored during the course of the study using the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS will be assessed in clinic at Screening, Baseline (V1), V10 (week 12), V13 (week 24) and the ET visits for the core part. For the extension part, the C-SSRS will be assessed in clinic at V14 (week 32), V21 (week 40), V24 (week 48), V26 (week 56), V27 (week 68), V28 (week 80), V30 (week 92), and the ET visits. For the additional extension part, the C-SSRS will be assessed in clinic at A1 (if needed), A2, A3, A4, A5, A6, A7, AF and the ET visits.

Two versions of C-SSRS will be used in this trial: Baseline/Screening C-SSRS with Lifetime and Past 12 Months lookback times at Screening and Baseline visits (V1), and Since-Last-Visit C-SSRS at all follow-up visits.

8.4 Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

8.4.1 Definition of AE

a. AE Definition:

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

b. Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected DDI.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, per se, will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action, per se, will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

c. Events not Meeting the AE Definition:

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

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

8.4.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- a. Results in death.
- b. Is life-threatening:
 - The term life-threatening in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- c. Requires inpatient hospitalization or prolongation of existing hospitalization:
 - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
 - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- d. Results in persistent or significant disability/incapacity:
 - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
 - This definition is not intended to include experiences of minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.
- e. Is a congenital anomaly/birth defect.
- f. Other situations:
 - Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical

events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following-up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see [Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal](#)). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 3: AEs and SAEs: Procedures for Recording, Evaluating, Follow-up, and Reporting](#).

8.4.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the beginning of the screening period until the follow-up visit at the time points specified in the SoA ([Section 1.3](#)).

All SAEs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in [Appendix 3: AEs and SAEs: Procedures for Recording, Evaluating, Follow-up, and Reporting](#). The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.4 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.5 Adverse Events of Special Interest

These AESIs are to be

recorded by the PI on the AE section of the CRF and should be transmitted to the Sponsor within the same timelines and in the same format as defined for SAEs.

8.4.6 Follow-up of AEs, SAEs, and AESI

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts.

Irrespective of the causal relationship to the study intervention, all AEs will be monitored with clinical observation or tests, and appropriately treated, until recovered/resolved, recovering/resolving, stabilization, the event is otherwise explained, or judged not to require further follow-up or the participant is lost to follow-up (as defined in [Section 7.3](#)).

All SAEs and AESIs will be followed until recovered/resolved, recovering/resolving, stabilization, the event is otherwise explained, or judged not to require further follow-up or the participant is lost to follow-up (as defined in [Section 7.3](#)).

Further information on follow-up procedures is provided in [Appendix 3: AEs and SAEs: Procedures for Recording, Evaluating, Follow-up, and Reporting](#).

8.4.7 Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to the Sponsor is essential, so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. SAEs should be reported to the Sponsor by the Investigator according to [Appendix 3: AEs and SAEs: Procedures for Recording, Evaluating, Follow-up, and Reporting](#).
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and Investigators.
- An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the other documents, and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.8 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention.
- Pregnancy will lead to participant exclusion.
- If a pregnancy is reported, the Investigator will record pregnancy information on the Pregnancy Report and submit it to the Sponsor or designee via email or confirmed

facsimile (fax) transmission within 24 hours of learning of the female participant pregnancy. The details of any pregnancy must be reported to the Sponsor or designee via email or confirmed facsimile (fax) transmission within 24 hours of obtaining the information.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in [Section 8.4.7 Regulatory Reporting Requirements for SAEs](#). While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.9 Overdose

There are currently no criteria for treatment of overdose. Blinded review of the safety data will be conducted on an ongoing basis to monitor for cases of overdose.

8.4.10 Cardiovascular and Death Events

The study will be terminated or halted temporarily by the Sponsor if any severe DILI case that causes death or transplant occurs and is considered related to study treatment.

8.4.11 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Any symptoms, complications, or outcomes associated with MSA (i.e., disease progression), but not qualifying as an AE, will be closely monitored and recorded throughout the study.

8.4.12 Safety Unblinding

The part of this study is a double-blind study in which participants/care providers/investigators/outcomes assessors are blinded to study intervention. The IVRS/IWRS is programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's

discretion, contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately of this occurrence. The date and reason for the unblinding must be entered in the eCRF.

The procedures for the medical emergency unblinding at a participant level are as follows:

- The PI has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the adverse event.
- The PI accesses the IWRS to retrieve the treatment assignment for the participant in question.
- [REDACTED]
- The PI must promptly document the decision and rationale and notify the sponsor as soon as possible.
- The concerned participant must be discontinued from the study treatment if a PI, study personnel performing assessments, or participant/caregiver is unblinded for the participant's treatment assignment.

8.5 Pharmacokinetics

Plasma PK sampling will be collected at before daily dose during V3 and V8 [REDACTED], and at before daily dose, $3h \pm 1h$, and $5h \pm 1h$ post daily dose during V10 and V13 [REDACTED] (see [Section 1.3](#)).

[REDACTED]

[REDACTED]

As needed, the efficacy, safety and PK data obtained in this study may be used to develop a population PK and PK/PD model. A PK report may be generated independently from the clinical study report for this study.

Pharmacokinetics assessments will not be performed in the extension part.

8.6 Pharmacodynamics

A statistical analysis plan (SAP), including details on analysis of exploratory pharmacodynamic biomarker endpoints, will be finalized prior to database lock.

Exploratory biomarker endpoints are described in [Section 9.3.5.1](#).

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8.10 Health Economics Outcomes Research, Medical Resource Utilization, and Health Economics

Health economics outcomes research, medical resource utilization, and health economics parameters will not be evaluated in this study.

9 STATISTICAL CONSIDERATIONS

An SAP will be finalized prior to database lock and will include more detailed descriptions of the statistical analyses outlined in this section.

9.1 Statistical Hypotheses

No inferential statistical hypotheses are planned to be tested.

9.1.1 Multiplicity Adjustment

Not applicable for this study.

9.2 Analysis Sets

The Safety Analysis Set (SAF) will be based on all participants who have signed the informed consent Form and who have received at least one dose of study treatment. Participants 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 will be used for all safety analyses.

The Full Analysis Set (FAS) will be the primary analysis set used for assessment of efficacy and will be based on all participants who have been randomized. This may include participants who have not been treated with ONO-2808 (i.e., following the Intention-To-Treat [ITT] principle). Participants 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.

9.3 Statistical Analyses

9.3.1 General Considerations

Descriptive summaries will be presented by study part (core, extension and additional extension) using mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and using count and percentage for categorical variables. Summary and analysis of data will be carried out using SAS® Version 9.4 or later software.

9.3.2 Handling of Missing Data

Every effort will be made to obtain data entry compliance in all critical fields during the course of the study. The study assumes 15% of randomized participants will experience missing data. Reasons for missing data will be collected and a distribution of the prognostic factors in subjects with and without missing data may be compared to identify any confounding factors. Details will be provided in the SAP.

9.3.3 Primary Endpoints Analysis/Safety Analysis

9.3.3.1 Definition of endpoints

The primary endpoints include incidence or change from baseline in each study part (core and extension) and overall, in the following assessments:

- Incidence and severity of treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs).
- Vital signs (blood pressure, pulse rate, temperature, respiratory rate).
- 12-lead electrocardiograms (ECGs); parameters such as, but not limited to, heart rate, RR, PR, QRS, QT, and corrected QT intervals (QTcF).
- Clinically significant abnormal physical examination findings.
- Clinically significant laboratory abnormalities (hematology, clinical chemistry, and urinalysis), including survey of drug-induced liver abnormalities.
- [REDACTED]
- Clinically abnormal findings in the Columbia Suicide Severity Rating Scale (C-SSRS).

9.3.3.2 Main Analytical Approach

TEAEs are defined as any AE occurring or worsening on or after the first dose of study treatment. Incidence of TEAEs, drug-related TEAEs, TEAEs resulting in study treatment discontinuation, TESAEs, and drug-related TESAEs will be tabulated by study part (core and extension) and overall by System Organ Class and Preferred Term, as defined by the Medical Dictionary for Regulatory Activities (MedDRA®), and by severity. For hematology and clinical chemistry data, summary statistics and changes from baseline from each study part (core and extension) will be calculated for continuous variables at each time point. Frequency distributions will be calculated for categorical variables at each time point. For vital signs, summary statistics and changes from baseline in each study part (core and extension) will be calculated at each time point. For ECG parameters (e.g., RR interval, QT interval, and QTc), summary statistics and changes from baseline in each study part will be calculated at each time point.

[REDACTED]

9.3.4 Secondary Endpoints Analysis

9.3.4.1 Definition of endpoints

The secondary endpoints include evaluation of the following assessments:

- Plasma concentration of ONO-2808.

9.3.4.2 Main Analytical Approach

Descriptive summary statistics will be calculated for ONO-2808 plasma concentrations, by dose level and time point in the core part.

9.3.5 Exploratory Endpoints Analysis

9.3.5.1 Definition of endpoints

The exploratory endpoints include change from baseline in each study part (core, extension, and additional extension) and overall, in the following assessments:

- UMSARS

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The exploratory endpoints include evaluating the following imaging parameters:

- MRI volumetric assessments of white and gray matter
- DTI for white matter abnormalities (core part and extension part only)

9.3.5.2 Main Analytical Approach

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9.3.6 Other Safety Analyses

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 (core and extension). In addition, a categorical summary of post-baseline clinically-significant abnormal laboratory results, at any time including unscheduled visits, will be provided in each study part. Similarly, a categorical summary of post-baseline clinically-significant abnormal vital sign results, at any time, including unscheduled visits, will be provided in each study part.

9.3.7 Other Analyses

The extent of drug exposure and demographic and baseline characteristics will be summarized using descriptive statistics and/or frequency counts in each study part (core and extension).

9.4 Interim Analyses

An interim analysis is planned after the last participant from the core part of ONO-2808-03 study rolls over to the extension part and completes V13 (week 24). All safety and exploratory efficacy endpoints will be included in the interim analysis, which will include comparison of changes from both the baseline of the core part and the extension part. Results from the interim analysis will be used for planning of future trials for ONO-2808. Details for the interim analysis will be outlined in the SAP.

9.5 Sample Size Determination

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

Sample size and statistical power were calculated for the overall treated cohort in the core part [REDACTED] in order to detect a transaminitis event rate as high as that seen during Phase I 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)ⁿ. 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:

$$\begin{aligned} (1 - [REDACTED])^n &= 0.05 \\ n \times \ln([REDACTED]) &= \ln(0.05) \\ n &= \ln(0.05) / \ln([REDACTED]) = [REDACTED] \text{ subjects (3 arms with } n = [REDACTED]) \end{aligned}$$

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.

Power for selected event rates, per treatment arm

Event Rate		Power	

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.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
 - Applicable ICH GCP guidelines.
 - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, investigational directions for use (IDFU), and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any Amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and substantial Amendments to the protocol, according to the applicable regulation, will require health authority approval prior to initiation, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR (if applicable), ICH guidelines (if applicable), the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The Investigator or the Investigator's representative (if applicable) will explain the nature of the study, including the risks and benefits, to the potential participant or their legally authorized representative, and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They or their LAR(s) will be required to sign and personally date a statement of informed consent that meets the applicable regulatory requirements, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained in order to enroll the participant in the study, along with the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and personally date the ICF.
- Participants must be re-consented to sign and personally date the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.
- Participants who request to discontinue study intervention will continue to follow-up as specified in the protocol. If the participant or his/her representative withdraws consent for the follow-up assessment, he/she should inform the Investigator in writing to the extent possible. Whether the withdrawal of consent is for treatment only in subsequent clinical studies, or for follow-up investigation after completion of clinical study procedure or for both, Investigators will record it in the original document such as medical records and record it in the eCRF. When assessing survival status (participant's survival or death) using public information, follow local law and instructions.

10.1.4 Data Protection

- Participants will be assigned a unique identification number by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the participant identification number only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5 Committees Structure

10.1.6 Dissemination of Clinical Study Data

- The Sponsor's policy for dissemination of clinical study data is described on the following websites:
 - https://www.ono.co.jp/company/policies/clinical_trial_data_transparency_policy.html
 - https://www.ono-pharma.com/company/policies/clinical_trial_data_transparency_policy.html

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator and study staff will promptly enter the data in the eCRF after completion of each observation of the participant, according to the provisions of the protocol for all

participants who have provided written informed consent to participate in the study. The study staff are permitted only to transcribe data from the source document. The Investigator is responsible for verifying that data entries, including audit trail and responses to queries, are accurate and correct by electronically signing the eCRF. An electronic signature has the same legal binding force as a handwritten signature, and electronically signed content cannot be repudiated later.

- Guidance on the completion of eCRFs will be provided separately.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques [REDACTED] are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator/institution for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor or designee, whichever is longer. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Location List.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source

documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

<https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission#p-1299>

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause, and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to, the following:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Any publication or presentation of the results of a study conducted under this protocol requires prior confirmation by the Sponsor. Publication of study results will be decided in consultation with the Sponsor.

10.2 Appendix 2: Clinical Laboratory Tests

- The blood samples for parameters outlined in [Table 10.2-1](#) will be collected at scheduled visits and timepoints (see [Section 1.3 Schedule of Activities \(SoA\)](#)).
- 
- The unscheduled blood samples collected for safety assessment and confirmation, as detailed in [Table 10.2-2](#) may be  to meet the required 48 hours safety confirmation period, if necessary. If a local sample is performed, the test results and the local laboratory normal range will be recorded in the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 5 Study Population](#) of the protocol.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- Reference values for laboratory tests will be recorded in the eCRF.

Table 10.2-1: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	· Platelet count	
	· Red blood cell (RBC) count	
	· RBC indices:	· Mean corpuscular volume (MCV) · Mean corpuscular hemoglobin (MCH) · %Reticulocytes
	· White blood cell (WBC) count with differential (count):	· Neutrophils · Lymphocytes · Monocytes · Eosinophils · Basophils
	· Hemoglobin	
	· Hematocrit	
Clinical chemistry ¹	· Blood urea nitrogen (BUN) · Glomerular filtration rate (GFR) · Potassium · Creatinine · Sodium	· Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) · Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) · Alkaline phosphatase ²

	· Calcium · Glucose · Total protein · Cholesterol · Triglycerides · Albumin · Phosphorus	· Total bilirubin (TBL), direct bilirubin (DBL) · Gamma-glutamyl transferase (GGT) · Lactate dehydrogenase (LDH) · Creatine phosphokinase (CPK)
Coagulation	· APTT · PT	· INR
Routine urinalysis	· Bilirubin · Ketones · Nitrites · Glucose · Leucocytes	· pH · Protein · Urobilinogen · Blood
Pregnancy testing	· Highly sensitive serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test (as needed for women of childbearing potential)³	
Other screening tests	· Serology (HIV antibody, hepatitis B surface antigen [HBsAg], HCV antibody, and SARS-CoV-2) · HbA1c · Neurological exam · Physical examinations	

¹ Details of liver chemistry stopping criteria and required actions and follow-up are given in [Section 7.1.2 Liver Chemistry Stopping Criteria](#) and [Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments](#). All events of ALT [or AST] 3 × ULN and TBL 2 × ULN (> 35% DBL) or ALT 3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy’s law), must be reported to [Sponsor] in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

² If alkaline phosphatase is elevated, consider fractionating.

³ Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC

Investigators must document their review of each laboratory safety report.

Table 10.2-2: Guidance on Monitoring of Participants with Elevated LFTs

Required Actions	ALT or AST $\geq 3 \times$ ULN	Potential Hy's Law Case (TBL $> 2 \times$ ULN with nR-value ≥ 5 or TBL $> 2 \times$ ULN with ALT or AST $\geq 3 \times$ ULN, but without Notable Increase in ALP to $> 2 \times$ ULN)	ALT Or AST $> 8 \times$ ULN	ALT or AST $> 3 \times$ ULN and INR > 1.5	ALT Or AST $> 3 \times$ ULN Accompanied by (General) Malaise, Fatigue, Abdominal Pain, Nausea, or Vomiting, or Rash with Eosinophilia	ALT Or AST $> 5 \times$ ULN, to $\leq 8 \times$ ULN	ALT Or AST $> 3 \times$ to $\leq 5 \times$ ULN (asymptomatic)	ALP $> 2 \times$ ULN (isolated)	Liver Related SAE	TBL $> 2 \times$ ULN (in the Absence of Known Gilbert Syndrome)	TBL $> 1.5 \times$ ULN to $\leq 2 \times$ ULN (Asymptomatic)	Jaundice (or Equivalent Term)	Any AE Event Potentially Indicative of a Liver Toxicity #	ALT or AST $\geq 10 \times$ ULN
Discontinue the study treatment immediately		√	√	√	√					##		√	√ Consider	√
Hospitalize, if clinically appropriate		√	√	√	√					√		√	√	√
If discontinuation criteria are met but the subject is not eligible for hospitalization, repeat LFTs within 48 to 72 hours		√	√	√	√					√		√	√	√
Establish causality ⁶		√	√	√	√	√*		√**		√		√	√	√
Complete liver eCRF		√	√	√	√	√ ($\geq 5x$)		√ ($\geq 2x$)	√	√		√	√	√
Repeat LFT within 48 hours. If elevation persists for more than 2 weeks, discontinue the study intervention						√								
Repeat LFT within 48 hours. If elevation persists, discontinue the study intervention								√		√				
Monitoring LFT weekly if trending up; then at least bi-weekly when trending down until resolution ⁵		√	√	√	√	√	√	√	√	√	√	√		√

Required Actions	ALT or AST $\geq 3 \times$ ULN	Potential Hy's Law Case (TBL $> 2 \times$ ULN with nR-value ≥ 5 or TBL $> 2 \times$ ULN with ALT or AST $\geq 3 \times$ ULN, but without Notable Increase in ALP to $> 2 \times$ ULN)	ALT Or AST $> 8 \times$ ULN	ALT or AST $> 3 \times$ ULN and INR > 1.5	ALT Or AST $> 3 \times$ ULN Accompanied by (General) Malaise, Fatigue, Abdominal Pain, Nausea, or Vomiting, or Rash with Eosinophilia	ALT Or AST $> 5 \times$ ULN, to $\leq 8 \times$ ULN	ALT Or AST $> 3 \times$ to $\leq 5 \times$ ULN (asymptomatic)	ALP $> 2 \times$ ULN (isolated)	Liver Related SAE	TBL $> 2 \times$ ULN (in the Absence of Known Gilbert Syndrome)	TBL $> 1.5 \times$ ULN to $\leq 2 \times$ ULN (Asymptomatic)	Jaundice (or Equivalent Term)	Any AE Event Potentially Indicative of a Liver Toxicity #	ALT or AST $\geq 10 \times$ ULN
Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)										√				
Required additional tests: Hepatitis A virus panel, Hepatitis B virus panel, Hepatitis C virus panel, Hepatitis E virus panel, CMV (cytomegalovirus) antibody immunoglobulin M, EBV (Epstein Barr Virus) panel ⁷ , ANA (anti-nuclear antibody) titer, ASMA (anti-smooth muscle antibody), AMA (antimitochondrial antibody), IgG (immunoglobulin G) level, Liver Ultrasound	√***													√

Abbreviations: ULN=upper limit of normal; ALT= alanine transaminase; AST= aspartate transaminase; ALP= alkaline phosphatase; INR=international normalized ratio; SAE=serious adverse event; AE=adverse event; eCRF=electronic case report form; LFT=liver function tests.

1. #: The events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.
2. ##: Discontinuation from study treatment is not required for individual cases, which will be closely monitored. However, if multiple cases arise during the study, the sponsor will do an aggregate review and if a new safety signal is detected, may consider discontinuation for at risk participants after further examination and discussion.
3. [REDACTED]

4. √**: If elevation persists, establish causality.
5. Resolution: is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at 3 subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.
6. PI should refer to the CIOMS Report on DILI for specific guidance on determining causality. ²⁵
7. EBV panel should include EBV heterophile antibody, EBV capsid antibody IgM, and EBV early antigen IgG.
8. √***: All additional liver tests listed are required when ALT or AST reaches $\geq 3\times\text{ULN}$ and where indicated, except for Liver Ultrasound, and should be performed as soon as possible. Liver Ultrasound is only required for ALT or AST $\geq 10\times\text{ULN}$. Please consult with the Safety Physician and Medical Monitor to determine repeat testing, especially as elevations occur.

10.3 Appendix 3: AEs and SAEs: Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Recording, Evaluating, and Follow-Up of AE and/or SAE

a. AE and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identification, except for the participant number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For AEs/SAEs, the event name, onset date and time, intensity, decision to continue study intervention, action taken, seriousness, causal relationship with study intervention, and outcome at the time of last observation (if recovered, date of recovery) will be recorded in the eCRF.

b. Assessment of Intensity:

The Investigator will assess the intensity for each AE and SAE reported during the study, and assign it to one of the following categories:

- **Mild:**
A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:**
A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- **Severe:**
A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

c. Causal Relationship with Study Intervention:

The causal relationship between an event and study intervention will be assessed on the following 2-point scale in consideration of the participant's condition, medical history, concomitant drugs, any causality other than the study intervention (such as risk factors), and temporal relationship between the event onset and the study intervention administration. AEs assessed as "1" will be handled as adverse drug reactions, and the rationale for "1" will be recorded in the eCRF.

1. Related: There is a reasonable causal relationship between study intervention administration and the AE.
2. Not related: There is not a reasonable causal relationship between study intervention administration and AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

d. Decision to Continue Study Intervention:

Should an AE occur, the decision of the Investigator on whether to continue administration of the study intervention will be classified into one of the following 6 categories and recorded. Note that the decision of the participant is not considered in these categories.

Judgment of the Investigator	Definition
Dose Not Changed	Continuation of the study intervention is judged to be possible by the Investigator.
Drug Interrupted	The study intervention should be temporarily interrupted in the opinion of the Investigator.
Dose Increased	The study intervention should be increased in the opinion of the Investigator.
Dose Reduced	The study intervention should be reduced in the opinion of the Investigator.
Drug Withdrawn	The study intervention should be terminated in the opinion of the Investigator.
Not Applicable	The event occurred after last dosing of study intervention.
Unknown	Action taken with the study intervention as per judgment of the Investigator is unknown.

e. Outcome of AE:

The outcome of an AE (symptom or abnormal laboratory finding) will be assessed according to the following criteria. If the event resolves, the resolution date will be determined. Otherwise, the outcome at the time of final observation will be determined.

Outcome	Criteria (For Information)
Recovered/Resolved	The symptom resolved, or the laboratory value normalized or returned to the pre-therapy intensity.
Recovering/Resolving	The event decreased in intensity, or the symptom showed an improving tendency.

Outcome	Criteria (For Information)
Not Recovered/Not Resolved	The symptom or the laboratory value has not improved.
Recovered/Resolved with Sequelae	The event resolved or was resolving, but with remaining symptoms of disability or other sequela.
Fatal	The participant died.
Unknown	The outcome cannot be assessed as one of the above because the participant is lost to follow-up or for other reasons.

f. Follow-up of AEs and SAEs:

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.2 Reporting of SAEs, Pregnancy and Overdose

Serious AEs, pregnancies or overdoses, whether related or not related to the study intervention, must be treated properly by the Investigator and reported to the Sponsor or designee within 24 hours of information being available. Serious AE data reporting method for this study is through the eCRF.

When new information is obtained, such as an addition/change that may affect the safety evaluation of already reported SAEs, the Investigator must report it to the Sponsor or designee within 24 hours after obtaining the information.

The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to the Sponsor (or designee). In this case, the paper form is transmitted via email or confirmed facsimile (fax). When paper forms are used, the original paper forms are to remain on site. The SAE information must be entered into the eCRF within 24 hours of the EDC system becoming available.

Pregnancies and overdose must be recorded on a paper Pregnancy Report and SAE Report Form, respectively, and transmitted via email or fax transmission. Further information on reporting procedures is provided in [Section 8.4 Adverse Events \(AEs\) Serious Adverse Events \(SAEs\), and Other Safety Reporting](#).

As necessary, the Sponsor will conduct assessment of the details, together with medical experts, and if medical experts request the submission of data such as scan images for safety evaluation,

the Sponsor will submit these data, with personal information redacted according to the regulations in the relevant countries.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Women of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche.
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below):
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
 - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly-effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
 - Permanent sterilization methods (for the purpose of this study) include:
 - Documented hysterectomy.
 - Documented bilateral salpingectomy.
 - Documented bilateral oophorectomy.
 - For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

10.4.2 Contraception Guidance

a. Male participants:

Non-vasectomized male participants must use an effective method of contraception from dosing on Day 1 until 100 days after the last administration of study intervention and agree not to donate sperm until 100 days after the last administration of study intervention.

b. Female participants:

Female participants must use an effective method of contraception from dosing on Day 1 until 40 days after the last administration of study intervention and have a negative pregnancy test at Screening.

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:
Highly-Effective Methods ^b That Have Low User Dependency: Failure rate of <1% per year when used consistently and correctly:
• Non-hormonal intrauterine device. • Bilateral tubal occlusion.
• Azoospermic partner (vasectomized or due to a medical cause). • Azoospermia is a highly-effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly-effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly-Effective Methods ^b That Are User Dependent: Failure rate of <1% per year when used consistently and correctly:
• Sexual abstinence. • Sexual abstinence is considered a highly-effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

The potential for liver injury and its signs and symptoms will be outlined in the informed consent document. Investigators and their designees should educate participants and their caregivers about the signs and symptoms of liver injury, such as abdominal pain, nausea, vomiting, loss of appetite, dark urine, yellow eyes, pruritis, or persistent fatigue. Should these symptoms occur in trial participants, either during the clinical trial or up to 60 days after receiving the last dose of the investigational agent, participants should report to the Investigator and seek immediate medical attention.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Study intervention re-challenge is not allowed in this study. A discontinuation of the study intervention should be clearly documented and reflected on the Drug Exposure eCRF panel. AE/SAEs will be reported as appropriate.

Frequent monitoring of liver function parameters in all participants is planned throughout this study. In the core part and for participants moving to active dose for the first time in the extension part, LFTs will be conducted at baseline, weekly for the first 6 weeks of dosing, bi-weekly over the next 6 weeks, and monthly thereafter. In the extension part, LFTs will be conducted every 2 months until week 60, then every 3 months.

In cases needing further investigations, such as for suspected DILI, unscheduled assessments/tests may be required (i.e., clinical, laboratory tests, imaging, and histological evaluation). Guidance on monitoring of participants with elevated LFTs is detailed in [Table 10.2-2](#). Data for such tests should be collected [REDACTED] For any laboratory assessments performed locally, clinical sites will ensure that local laboratory test results are accompanied by reference range values and units of measure. These local laboratory test results and the local lab normal ranges will be recorded in the eCRF and made available to the IDMC in a timely manner to facilitate the IDMC's adjudication of a suspected case.

Completed subject level data reporting for any suspected DILI case will be submitted to the Agency for review.

10.6 Appendix 6: Country-specific Requirements

10.6.1 Drugs used in the Clinical Trial

10.6.1.1 Investigational Intervention

ONO-2808

10.6.1.2 Drugs used in the Clinical Trial other than Investigational Intervention

Not applicable.

10.7 Appendix 7: Clinical Outcomes Assessment Descriptions

UMSARS

Unified Multiple System Atrophy Rating Scale (UMSARS) measures disease progression in MSA. There are four parts: historical, motor examination, autonomic examination, and global disability scale. The scale takes about 30-45 minutes to complete.

In the core part, it will be administered at Screening, Baseline (V1), V10 (week 12), V13 (week 24), and the early termination (ET) visits.

In the extension part, it will be administered at V14 (week 32), V21 (week 40), V24 (week 48), V26 (week 56), V27 (week 68), V28 (week 80) and the ET visits.

In the additional extension part, it will be administered at A1 (if needed), A2, A3, A4, A5, A6, A7 and the ET visits.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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Brain and Liver MRI

A Brain MRI will be used for exploratory analyses including volumetric assessments of white and gray matter, and DTI for white matter abnormalities. A Liver MRI will be used to monitor DILI. Brain and Liver MRI scanning can be combined.

In the core part, Brain and Liver MRI scanning will be completed before the baseline visit (V1), and the follow up MRI scanning will be performed at V13 (week 24) or the ET visit. Unscheduled Liver MRI should be completed as needed if persistent transaminitis is observed.

In the extension part, Brain MRI scanning will be completed at V24 (week 48) and V28 (week 80) or the ET visit. Unscheduled Liver MRI should be completed as needed if persistent transaminitis is observed.

In the additional extension part, Brain MRI (only volumetric assessments of white and gray matter, and no DTI) scanning will be completed at A5 or the ET visit. Unscheduled Liver MRI should be completed as needed if persistent transaminitis is observed.

10.8 Appendix 8: Protocol Amendments

10.8.1 Protocol Amendment #1 (protocol version 1.0 to 2.0)

Protocol Section	Page	Changes
		Editorial changes were made throughout the document for clarity and quality.
		[REDACTED]
		[REDACTED]
		[REDACTED]
		[REDACTED]
		[REDACTED]
		[REDACTED]
		[REDACTED]
8.3.7 Suicidal Ideation and Behavior Risk Monitoring	53	Typographical error of the timepoints was corrected. Changes: Baseline assessment of suicidal ideation and behavior/intervention-emergent SIB will be monitored during the course of the study using the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS will be assessed in clinic at Screening, Baseline, V10 (week 12), V13 (week 24) and the ET visits. Two versions of C-SSRS will be used in this trial: Baseline/Screening C-SSRS Lifetime at Screening and Baseline visits and Since-Last-Visit C-SSRS at all follow-up visits.
		[REDACTED]
		[REDACTED]
		[REDACTED]

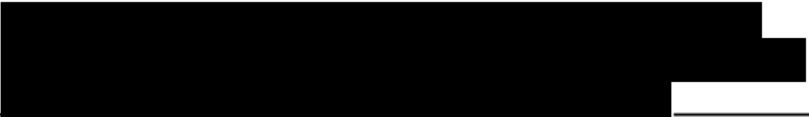
10.7 Appendix 7: Clinical Outcomes Assessments Descriptions	84	Details were added for each clinical outcomes assessment, including description of the scale, the version being used, and the timepoints for administration.

10.8.2 Protocol Amendment #2 (protocol version 2.0 to 3.0)

Protocol Section	Page	Changes
		Editorial changes were made throughout the document for clarity and quality.
1.3 Schedule of Activities (SoA)	20	Clarification that informed consent should be done at screening visit only in the SoA.
1.3 SoA footnote #5	22	Added language to clarify blood sampling across visits. <i>“At UNS visits, LFTs required when criteria met per LFT guidance; any other test may be included per PI discretion at UNS visit only. At home visits, only LFTs are required.”</i>
8 Study Assessments and Procedures	50	Added mention of an investigator site file.
1.3 SoA footnote #10	22	Added a footnote to the SoA to clarify that covid testing is optional per site requirements and will be performed at local labs only.
Table 10.2-1: Protocol-required Safety Laboratory Tests	73	Noradrenaline urine analyte was removed from the list of exploratory analyses.
5.1 Inclusion Criteria	33	Clarification of eligibility for optional procedures was added: While participants who require a legally authorized representative to provide consent are eligible in the main study per Inclusion Criterion #9, these participants will not be eligible for the optional biomarker sub-study.

[illegible]

10.8.3 Protocol Amendment #3 (protocol version 3.0 to 4.0)

Protocol Section	Page	Changes
		Editorial changes were made throughout the document for clarity and quality.
Section 1.1 Protocol Synopsis, Overall Design Synopsis	16	Clarification was made that our sites will include those from Japan in addition to the US.
		 
Section 10.2 Appendix 2: Clinical Laboratory Tests	72	Additional language was added to clarify that local lab testing is permitted for scheduled visits if deemed necessary.
Table 10.2-2 Guidance on Monitoring of Participants with Elevated LFTs	74-76	Two new scenarios were added: “If discontinuation criteria are met but the subject is not eligible for hospitalization, repeat LFTs within 48 to 72 hours.” <u>Required additional tests for cases of ALT or AST > 10 x ULN:</u> Hepatitis A virus panel, Hepatitis B virus panel, Hepatitis C virus panel, Hepatitis E virus panel, CMV (cytomegalovirus) antibody immunoglobulin M, EBV (Epstein Barr Virus) panel⁷, ANA (anti-nuclear antibody) titer, ASMA (anti-smooth muscle antibody), AMA (antimitochondrial antibody), IgG (immunoglobulin G) level, Liver Ultrasound Footnote #2 was modified: “2. ##: Discontinuation from study treatment is not required for individual cases, which will be closely monitored. However, if multiple cases arise during the study, the sponsor will do an aggregate review and if a new safety signal is detected, may consider discontinuation for at risk participants after further examination and discussion.” 

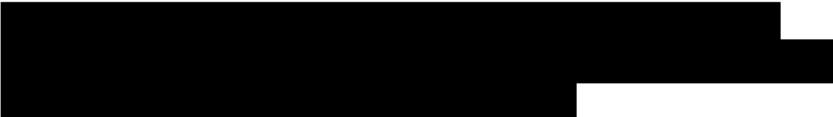
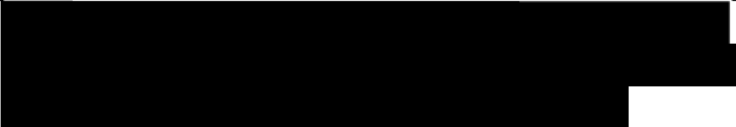
		Footnotes #6 and #7 were added: “6. PI should refer to the CIOMS Report on DILI for specific guidance on determining causality.²⁵” (See Reference #25 added.) “7. EBV panel should include EBV heterophile antibody, EBV capsid antibody IgM, and EBV early antigen IgG.”
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10.8.4 Protocol Amendment #4 (protocol version 4.0 to 5.0)

Protocol Section	Page	Changes
		Editorial changes were made throughout the document for clarity and quality.
		Incorporation of the extension part into the core part protocol was completed throughout the document.
Figure 1.2-2: Study Design, Extension Part	21	This figure was added to illustrate the design of the extension part.
Figure 1.2-3: Study Design	22	This figure was added to illustrate the design of the entire study, including the core and extension parts.
Figure 1.2-5: Study Flow, Extension Part	23	This figure was added to illustrate the visit schedule of the extension part.
Table 1.3-1 Schedule of Activities Table, Core Part; Footnote #9	26	The following language was added to allow for a wider range of time to conduct the MRIs before the baseline visit. <i>“9. Brain and Liver MRI scanning can be combined; imaging studies may be performed once the principal investigator confirms eligibility based on screening visit examination and safety work-up. It is the responsibility of the Principal Investigator to review the formal central reading of the imaging studies to ascertain final eligibility towards randomization. It is preferred that the baseline MRI scanning should be completed within 2 weeks prior to the start of dosing, however 4 weeks prior to the start of dosing is permitted.”</i>
Table 1.3-2 Schedule of Activities Table, Extension Part	27	Table 1.3-2 was added to describe the extension part schedule of activities.
Table 1.3-3 Schedule of Activities, Extension Part by Group and Visit	29	Table 1.3-3 was added to describe in detail the extension part schedule of activities for placebo and active groups, by visit.
3 Objectives and Endpoints	43	A second column was added to the table to describe the endpoints for the extension part.
5.1 Inclusion Criteria, #11	52	<i>“11. Patients vaccinated for SARS-CoV-2 (received primary series of COVID-19 vaccine) prior to Screening or history of SARS-CoV-2 infection documented by the PI.”</i>
5.2 Exclusion Criteria, #14	54	Edited to include the “F” to indicate QT corrected for heart rate by Fridericia's cube root formula should be utilized regarding the

		criterion. <i>“14. Confirmed absolute QTcF > 450 msec for males and > 470 msec for females and/or an increase of > 60 msec on repeated ECGs performed at least 2 minutes apart.”</i>
Table 6.1-3 Study Arm(s) for the Extension Part, Rollover Period	59	Table describing Study Arm(s) for the Extension Part, Rollover Period added.
Table 6.1-4 Study Arm(s) for the Extension Part, Open-Label Extension Period	60	Table describing Study Arm(s) for the Extension Part, Open-Label Extension Period added.
8.3.4 Electrocardiograms	74	Language was modified to clarify that a repeat ECG is required considering the average of the 3 measurements of QTc and not a single measurement out of the triplicate measures. <i>“The ECG will be repeated if the average QTc exceeds 500 msec or >60 msec change from baseline...”</i>
8.3.7 Suicidal Ideation and Behavior Risk Monitoring	75	Clarification of lookback times in C-SSRS was added. <i>“Two versions of C-SSRS will be used in this trial: Baseline/Screening C-SSRS with Lifetime and Past 12 Months lookback times at Screening and Baseline visits, and Since-Last-Visit C-SSRS at all follow-up visits.”</i>
8.4.1 Definition of AE	76	The <i>Definition of Solicited and Unsolicited AEs</i> section was removed as this type of AE does not apply to this study.
9.4 Interim Analysis	86	Language was added to describe the interim analysis planned after all participants complete the core part: <i>“An interim analysis is planned after the last participant from the core part of ONO-2808-03 study rolls over to the extension part and completes V13 (week 24). All safety and exploratory efficacy endpoints will be included in the interim analysis, which will include comparison of changes from both the baseline of the core part and the extension part. Results from the interim analysis will be used for planning of future trials for ONO-2808. Details for the interim analysis will be outlined in the SAP.”</i>

10.8.5 Protocol Amendment #5 (protocol version 5.0 to 6.0)

Protocol Section	Page	Changes
		Editorial changes were made throughout the document for clarity and quality.
		Incorporation of the additional extension part into the core and extension parts protocol was completed throughout the document.
		
Figure 1.2-2: Study Design, Extension Part	21	This figure was updated to include the additional extension part.
Figure 1.2-4: Overall Study Design	23	This figure was updated to include the additional extension part.
Figure 1.2-6: Study Flow, Extension Part	24	This figure was updated to include the additional extension part option at the conclusion of the existing extension part.
Table 1.3-1: Schedule of Activities, Core Part, Footnote 12	25	Clarification of the visit sequence is clarified for participants with elevated LFTs that meet IP discontinuation criteria.
Table 1.3-2: Schedule of Activities, Extension Part, Footnote 9	28	The following language was added to clarify a permissible delay in visit schedule due to administrative needs. <i>“It is permissible to delay the final Safety Follow-up visit, so the participant stays an active participant in the study, until the new protocol amendment for the Additional Extension is implemented at the site.”</i>
Table 1.3-2: Schedule of Activities, Extension Part, Footnote 10	28	Clarification of the visit sequence is clarified for participants with elevated LFTs that meet IP discontinuation criteria.
Section 8.4.12 Safety Unblinding	91	Details of Safety Unblinding procedures were added.
		

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Table 10.2-2 Guidance on Monitoring of Participants with Elevated LFTs	107	A new column and footnote 8 were added to describe the additional liver tests required when <u>ALT or AST $\geq 3 \times \text{ULN}$</u> is reached: <i>“8. √***: All additional liver tests listed are required when ALT or AST reaches $\geq 3 \times \text{ULN}$ and where indicated, except for Liver Ultrasound, and should be performed as soon as possible. Liver Ultrasound is only required for ALT or AST $\geq 10 \times \text{ULN}$. Please consult with the Safety Physician and Medical Monitor to determine repeat testing, especially as elevations occur.”</i>
[REDACTED]	[REDACTED]	[REDACTED]

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