Official Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of ASN51 in Adults With Early Alzheimer's Disease
NCT Number:	NCT06677203
Document Date:	Protocol Version 2: 07-Oct-2024

ASCENEURON
A Neurodegeneration Therapeutics Company

CLINICAL TRIAL PROTOCOL

Protocol Full Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of ASN51 in Adults with Early Alzheimer's Disease
Protocol Number:	ASN51-201
Protocol Acronym:	*[not yet assigned / none]*
Short Title:	ASN51 in Adults with Early Alzheimer's Disease
Current Version:	Version 2.0, 07 October 2024
Amendment Number:	Amendment 1.0
Amendment Scope:	Update to schedule of events and inclusion/exclusion criteria; minor clarifications
Investigational Product:	ASN51
Trial Phase:	Phase 2
Sponsor:	Asceneuron S.A. EPFL Innovation Park Bâtiment B, CH-1015 Lausanne SWITZERLAND
Regulatory Identifiers:	IND: 153714 ClinicalTrials.gov: *not yet assigned* EudraCT: *not yet assigned*

Sponsor Signatory:

[redacted] October 10, 2024

[redacted] MD
[redacted]
Asceneuron SA

Date

Medical Monitor: [redacted] MD
Email: [redacted]
Phone:

Serious Adverse Event Reporting:

Refer to Safety Management Plan for reporting instructions

Compliance Statement:

This clinical trial is to be performed in compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements.

Confidentiality Statement:

This document contains confidential and proprietary information; the information contained within may only be used for the purpose of conducting the trial. The information is intended solely for the use of the investigator, trial personnel, and applicable Institutional Review Boards or Independent Ethics Committees. Information in this document shall not be otherwise disclosed without prior written consent from Asceneuron SA.

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1.1 Protocol Synopsis

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<tr><td>Study Rationale</td><td>The purpose of this Phase 2 trial is to evaluate the safety, tolerability, and effect on biomarkers of disease pathophysiology and pathology, pharmacokinetics (PK), and preliminary effects on measures of clinical efficacy of multiple doses of ASN51 in adult participants with early Alzheimer's disease (AD).</td></tr>
<tr><td>Objectives & Endpoints</td><td>The primary and secondary objectives for the trial relate to the double-blind (DB), placebo-controlled, part of the study. Objectives and endpoints for the Long-term Extension (LTE) are exploratory and are outlined in the Study Protocol.
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>To evaluate the safety and tolerability of daily doses of ASN51 as compared with placebo in participants with early AD</td><td>• Incidence and severity of AEs
• Changes from baseline in laboratory safety assessments (including clinical chemistry, hematology, urinalysis, and serum hormone markers)
• Changes from baseline in vital signs, 12-lead electrocardiograms, and physical (including neurological) examinations
• Changes from baseline in C-SSRS</td></tr>
<tr><td colspan="2">Key Secondary</td></tr>
<tr><td>To evaluate the effect of daily doses of ASN51 as compared with placebo on the pathophysiology of early AD
To evaluate the effect of ASN51 versus placebo in change from Baseline to Week 24 on the pathophysiology of early AD</td><td>• Change from baseline through Week 24 in CSF pTau217
• Change from baseline through Week 24 in CSF total tau protein
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<tr><td>Other Secondary</td><td></td></tr>
<tr><td>To evaluate the effect of daily doses of ASN51 as compared with placebo on tau pathology in early AD</td><td>Change from baseline through Week 24 in MK-6240 tau PET signal</td></tr>
<tr><td>To evaluate the pharmacokinetics of ASN51 in early AD</td><td>Trough (C_{min}) at steady state and maximum (C_{max}) concentration of ASN51 in plasma at steady state through Week 24</td></tr>
<tr><td colspan="2">AD = Alzheimer's disease; AE = adverse event; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; PET = positron emission tomography.</td></tr>
</table></td></tr>
</table>

Study Design	• Multi-site, placebo-controlled, double blind, randomized, parallel group design with a randomized, parallel group LTE period.
Study Intervention	• ASN51 orally, [redacted] once daily.
Control/Comparator	• Placebo capsules matched in color, shape, size, and number of capsules administered.
Intervention Assignment Method / Arms	• Randomized 1:1:1 to once daily ASN51 [redacted], ASN51 [redacted], or placebo (n = 26/dose level) • Randomization stratified by baseline Alzheimer's treatment (symptomatic treatment [with an acetylcholinesterase inhibitor or memantine] versus no), and APOE4 status (carrier or non-carrier) • Following the 24-week DB Intervention Period, participants randomized to placebo will receive ASN51 (randomized 1:1 to [redacted]) during the dose-blind LTE Period. Participants initially randomized to ASN51 will continue at the DB-assigned dose level.
Population / Sample Size	• Adults (50 to 80 years) with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, collectively termed early Alzheimer's disease, with plasma pTau217 positivity as evidence of amyloid pathology • Approximately 78 participants are planned across three arms (n = 26 per arm). • Assuming a 20% dropout rate, approximately 21 participants per arm are expected to complete the study.
Key Eligibility Criteria	*Key Inclusion Criteria* • Male or female age 50 to 80 years • A clinical diagnosis of AD at either the mild cognitive impairment or mild AD dementia stage per National Institute on Aging and the Alzheimer's Association, consistent with Stage 3 and Stage 4 in the FDA draft guidance for early AD • Mini-Mental State Examination score of 20 to 28 (inclusive) • A plasma pTau217 result consistent with the presence of amyloid pathology (defined as > 0.18 pg/mL) • Must have a care partner who, in the Investigator's judgment, has frequent and sufficient contact with the participant (at least 10 hours/week) as to be able to provide accurate information about the participant's cognitive and functional abilities. The care partner must be literate and provide informed consent. *Key Exclusion Criteria* • Any medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause to the participant's cognitive impairment (e.g., current history of substance abuse, uncontrolled vitamin B12 deficiency or abnormal thyroid function, stroke or other cerebrovascular condition, normal pressure hydrocephalus, Parkinson's disease, Lewy body dementia, cerebral amyloid angiopathy, frontotemporal dementia) or could lead to discontinuation, lack of compliance, interference with study assessments, or safety concerns

	• Non-amnestic presentation of AD as judged by the Investigator • Woman of childbearing potential (per CTFG 2020) • Positive urine drug test at Screening. Testing positive for benzodiazepines or opioids in urine drug testing is permitted if determined by the Investigator to be due to appropriate medical use and not drug abuse. • Any prior or ongoing exposure to active or passive anti-amyloid immunotherapy, anti-tau immunotherapy, an anti-tau antisense oligonucleotide or gene therapy, or O-GlcNAcase inhibitor • Requires use of anticoagulants during trial participation • Any evidence of hepatic impairment (Child Pugh classification B and C are excluded) • Requires use of moderate or strong CYP3A4 inhibitors during trial participation • Requires use of moderate or strong CYP2C19 inhibitors during trial participation Additional eligibility criteria are described in the protocol.
Duration of Participation	Up to approximately 76 weeks, including: • A pre-screening period of up to 12 weeks (within 12 weeks of randomization) • A screening period of up to 8 weeks (within 8 weeks of randomization) • A placebo-controlled DB Intervention Period of 24-weeks • An LTE period of 36 weeks • A follow-up period of 4 weeks.

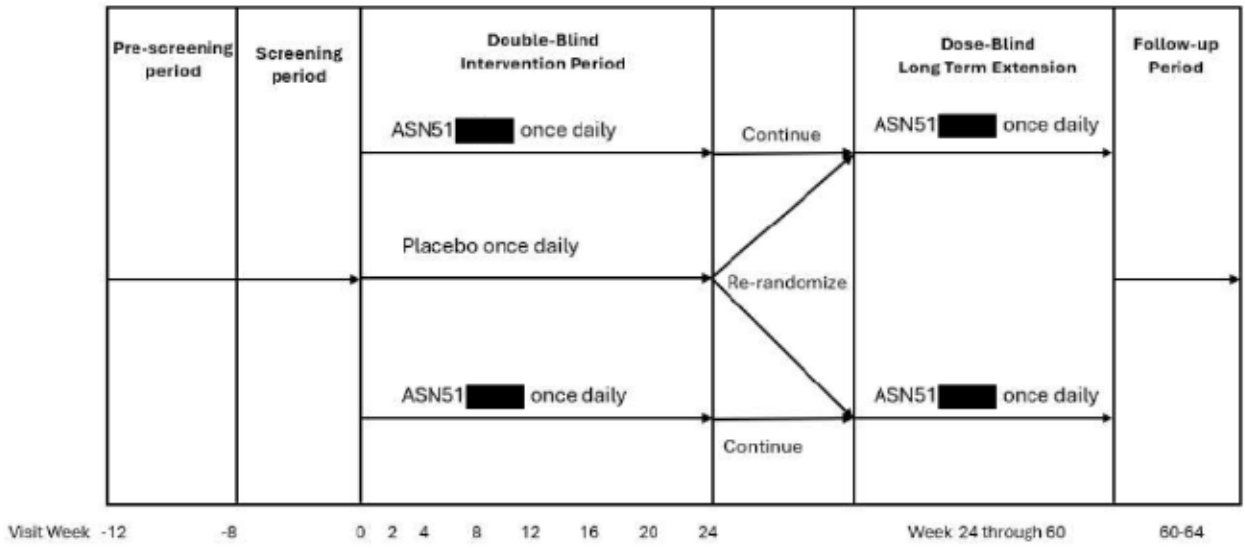
Trial Periods	• Prescreening period of up to 12 weeks, which includes the collection of medical history and plasma sample for pTau 217 and APOE genotype, may occur prior to the Screening period
	• Screening period of up to 8 weeks
	• Double-blind Placebo-Controlled Intervention Period (24 weeks, Week 1 to end of Week 23)
	  ○ Visits every 2 to 4 weeks; each visit may take place over more than 1 day if necessary
	• Long-term Extension Period (36 weeks; Weeks 24 to Week 60)
	  ○ Visits every 2 to 4 weeks from weeks 24 to 48 and then every 6 weeks; each visit may take place over more than 1 day if necessary.
	Participants who withdraw from the study prematurely are to return to the study site for an Early Termination (ET) Visit and assessments and for the Follow-up Safety Visit 4 weeks after the last administration of study intervention.

Statistical Methods	Trial data will be reported using summary tables, figures, and data listings. Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, median, minimum, and maximum will be provided. For discrete data, incidence and percentages will be provided. Statistical tests will be 1-sided at the alpha level of 0.10, unless stated otherwise. P-values will be used descriptively and will have no inferential value. Two sets of analyses will be conducted. The first set of analyses will be conducted after all participants have had the opportunity to complete the Week 24 assessment

	or have discontinued the study (primary analysis). The second set of analyses will be conducted when all participants have had the opportunity to complete the LTE or discontinued the study (final analysis). Both analyses will use similar methods: • Randomization stratified by baseline Alzheimer's treatment (symptomatic treatment use versus no current symptomatic treatment use), and APOE4 status (carrier or non-carrier). • For endpoints collected only once post-baseline, changes from baseline will be analyzed using an analysis of covariance model with a fixed effect term for randomized treatment group and the continuous covariate of the baseline value of the variable being analyzed. The model will also be stratified for the randomization stratification factors (i.e., APOE4 status and use of AD medication). Least squares (LS) mean estimates will be presented by treatment group along with the difference between each dose and placebo and the associated 90% and 80% 2-sided confidence intervals (CIs) and 1-sided p-value. • For endpoints collected multiple times post-baseline, changes from baseline will be analyzed using a restricted likelihood-based mixed effects model for repeated measures. Change from baseline will be fit as the dependent variable. Independent variables included in the analysis model will be randomized treatment group, visit, treatment by visit interaction, and the continuous covariates of the baseline value of the variable being analyzed. The model will also include the interaction between randomization stratification factors as a fixed effect. Within participant error will be modelled via an unstructured covariance matrix. LS mean estimates will be presented by treatment group over time along with the difference between each dose and placebo and the associated 90% and 80% 2-sided CIs and 1-sided p-value. The principal focus of inference will be the 24-week time point. No formal interim analysis is planned.
Committees	• A Safety Review Committee will review ongoing safety and tolerability data as described in a Charter.

1.2 Trial Schema

Figure 1 Trial Schema



1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening Period

Visit:	Screening
Screening Window (Days):[a,b]	
Tier 1 (Prescreening Period)	From Week -12
Abbreviated (or full) informed consent (participant)[c]	X
Assign Participant Number in IWRS	X
Demographics, medical history, preliminary eligibility review[d]	X
MMSE	X
Tier 2 (Prescreening Period)[d]	From Week -12
Plasma pTau 217	X
Blood for APOE genotype	X
Tier 3[e] (Screening Period)	Week -8 through Day -1
Full informed consent – participant & study partner[e]	X
Inclusion/exclusion criteria review	X
CDR-SB	X
Physical examination (including neurological), height, weight	X
Prior medications	X
Vital signs	X
Electrocardiogram (triplicate)[f]	X
C-SSRS [g]	X
Follicle-stimulating hormone (if applicable)[h]	X
Clinical chemistry, hematology, coagulation panel, urinalysis, urine drug screen	X
Viral screen (HbsAg, hepatitis C antibody test)[i]	X
Tier 4[j] (Screening Period)	Week -8 through Day -1
MRI[k]	(X)

AD = Alzheimer's disease; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; EU = European Union; FSH = follicle-stimulating hormone; HBsAg = Hepatitis B virus surface antigen; IVDR = in vitro diagnostic regulation; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography

Consult Section 8 for guidelines on procedures and assessments. Consult the Study Reference Manual for additional information, including a recommended order of (specific) assessments for each visit.

a The Screening Period may be up to 8 weeks in duration to allow for the completion of all screening assessments and for the evaluation of all laboratory, ECG, and imaging tests. Screening procedures will be completed over multiple days. If additional time is required, this will be considered and approved on a case-by-case basis by the Sponsor Medial Monitor.

b A non-contrast brain MRI is performed as the final test for eligibility. If a brain MRI scan is not available within the screening window (and a recent MRI is not available for eligibility determination), the Screening Period may be extended, if all other eligibility criteria have been met, by up to 14 days to provide additional time for the MRI results to become available. If the screening window is extended for an individual, repeat clinical chemistry and hematology laboratory tests so results are available within 6 weeks of the Day 1 visit. Results of the repeated laboratory tests are to be reviewed by the Investigator or a qualified designee for final assessment eligibility.

c An abbreviated screening informed consent may be utilized to conduct prescreening (i.e., Tier 1 and Tier 2) procedures, if allowed by the investigative site. Consent should include APOE genotyping. Generally, prescreening consent does not require the study partner; however, if, in the Investigator's opinion, a participant lacks capacity to consent, then the written informed consent of a legal representative should be obtained.

d Participants who meet Tier 1 eligibility criteria, including MMSE, should proceed to Tier 2 (plasma pTau217 and APOE genotype). Tier 1 and Tier 2 assessments may take place on the same day. The time and date of the plasma pTau217 test should be recorded on the Lab Requisition Form. The plasma pTau217 eligibility result is to be reported to the site. If the plasma pTau217 result does not meet criteria for eligibility, the participant is not to complete any additional screening. If plasma pTau217 is not available due to local regulations, an AD diagnostic test performed within no more than 52 weeks of screening that has been approved by the relevant local regulatory authority may be substituted (e.g., an IVDR-compliant assay such as amyloid PET or CSF ab42/40 in EU countries performed within 52 weeks of screening); the participant may be included if the result is interpreted by the Investigator as consistent with the pathological presence of amyloid beta in the brain. The result of any substituted test should be recorded in the participant's eCRF. APOE genotype may also be done at Tier 3 if not feasible to complete at Tier 2 but must be completed prior to randomization.

e If informed consent for the full study is not obtained at Tier 1 and an abbreviated consent form was used for Tier 1 and Tier 2 screening assessments, obtain full informed consent prior to initiation any Tier 3 screening procedures.

f ECGs should be taken supine in triplicate at approximately 1-minute intervals. Participants should rest for at least 5 minutes in the supine position before ECGs are taken.

g The "Screen Version" questionnaire will be administered at Screening. The "Since Last Visit" questionnaire will be administered at all subsequent visits.

h Required for females only. Females of non-childbearing potential are defined as meeting one of the following criteria: postmenopausal (defined as 12 months of spontaneous amenorrhea with other identifiable cause or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL) or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy confirmed by documentation.

i Participants with a suspected or confirmed past history of Hepatitis C are to have hepatitis C antibody test at V1 and are excluded if the test is positive.

j Participants may proceed to Tier 4 *only* after all criteria from Tier 1, 2, and 3 have been met.

k May be scheduled earlier at the Sponsor's discretion to facilitate timely scheduling. Submit the MRI to the central MRI vendor for final determination of eligibility. Results of centrally read MRIs will be used for data analysis; results will be communicated back to the site.

Table 2 Schedule of Activities: Double-blind Intervention Period

Visit:	Day 1[a, b]	Day 14	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	ET[c]	FU[d]
Visit Window (Days):	-	-4	±7	±7	±7	±7	±7	±7	±7	4 weeks (+14 days) post last dose
Inclusion/exclusion criteria review	X									
Contact IWRS, randomization	X									
Physical Examination (including neurological) and Weight	X		X		X			X	X	
Previous/Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Dispense/Review ASN51 Compliance[e]	X		X	X	X	X	X	X	X	
Efficacy Measures										
ADAS-Cog13[f]	X				X			X	X	
CDR-SB[f]	X				X			X	X	
MMSE[f]	X				X			X	X	
Safety Assessment										
Adverse Events[g]	X	X	X	X	X	X	X	X	X	X
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X
Laboratory Specimens[i]										
Clinical chemistry, hematology	X	X	X	X	X	X	X	X	X	X
Coagulation panel [j]	X						X		X	
Urinalysis	X		X		X			X	X	
Serum hormone markers	X		X		X			X	X	
Plasma for ASN51 PK[k,l]	X		X[k]		X[k]			X[k]	X	
Blood for pharmacogenomics[m,n]	X								X	
Plasma for biomarker storage[m]	X		X		X			X	X	
CSF for ASN51, biomarker storage[m]	X							X	X	
Other Safety Measures										
Vital signs[o]	X	X	X	X	X	X	X	X	X	(X)
ECG in triplicate[p]	X	X	X	X	X	X	X	X	X	(X)
Imaging Assessments										
^{18}F MK-6240 PET scan[q]	X							X	X	
Brain MRI[r]	(X)[r]							X	X	

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog13 = Alzheimer's Disease Assessment Scale – Cognitive Behavior Subscale 13; CDR-SB = Clinical Dementia Rating – Sum of Boxes; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale;

Visit:	Day 1[a, b]	Day 14	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	ET[c]	FU[d]
Visit Window (Days):	-	-4	±7	±7	±7	±7	±7	±7	±7	4 weeks (+14 days) post last dose

ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; EU = European Union; FSH = follicle-stimulating hormone; FU = follow-up; HBsAg = Hepatitis B virus surface antigen; IVDR = in vitro diagnostic regulation; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics.

Consult Section 8 for guidelines on procedures and assessments. Consult the Study Reference Manual for additional information, including a recommended order of (specific) assessments for each visit.

a Confirm that all Screening Visit eligibility criteria have been met before proceeding to any Day 1 activities.

b Schedule all remaining visits at Day 1 visit. Visits may take more than 1 day but should take place as close to the target date as possible. Participants must complete biomarker assessments (e.g., MRI, tau PET, CSF, and plasma) before proceeding to randomization.

c Early termination eCRFs should be completed if a participant discontinues before the Week 24 Visit. Schedule FU visit 4 weeks after the last dose of study intervention.

d Schedule the FU visit 4 weeks after the last dose of study intervention for safety assessment. The FU visit may be conducted by phone; however, any participant with an ongoing AE, or history of abnormal ECGs should be monitored by the Investigator and managed appropriately (with an in-clinic visit, including vital signs and ECG, if necessary).

e ASN51 should be taken once daily in the morning with or without food. The first dose should be taken at the clinic visit under supervision. Participants should be instructed to bring all study medication to the site at each indicated visit to assess compliance. For ET visit, no study intervention should be dispensed.

f Whenever performed on the same day, cognitive and functional assessments (ADAS-Cog13, CDR-SB, and MMSE) are to be performed before procedures that may be stressful for participants (for example, MRI, PET, blood draw, or CSF sampling).

g Any clinically significant changes from baseline in the physical examination should be noted as an AE.

h "Screen Version" questionnaire will be administered at Screening. The "Since Last Visit" questionnaire will be administered at all subsequent visits.

i Unscheduled laboratory tests may be performed at any time at the discretion of the Investigator if clinically indicated for a suspected AE.

j Record date and times of sample collection on the Lab Requisition Form. Obtain within 12 weeks of all lumbar punctures to confirm coagulation status.

k Weeks 4, 12, and 24 visits only: Participants will be contacted by telephone 1 day before scheduled PK sampling to remind them not to take trial intervention on the morning of their next visit, and to instead bring the dose to clinic to take under supervision. During the call, participants will be asked what time their study medication was taken that day, and the site is to record the last dose administration time prior to the PK sampling visit.

l Day 1, Week 4, Week 12, and Week 24 visits: A pre-dose ASN51 plasma sample will be taken. The actual time of dose administration in the clinic should be recorded in the participant's eCRF. A post-dose sample will also be obtained 1.5 to 4 hours after the participant takes the dose of trial intervention at the site and sites will record if the participant eats a full meal, as judged by the Investigator, within ± 2 hours of the dose administration.

m Blood and CSF for biomarker storage and blood for pharmacogenomics will be obtained, unless collection and/or transportation of the sample is prohibited due to local regulations. At the Day 1 visit, participants must have completed the blood and CSF collection procedures before randomization.

n The pharmacogenomic sample may be taken at a later visit if it cannot be collected at Day 1 Visit.

o Obtain vital signs while participant has been in a seated position for at least 5 minutes, preferably before other invasive procedures (e.g., blood draws, lumbar puncture).

p ECGs should be taken in triplicate at approximately 1-minute intervals. Participants should rest for at least 5 minutes in the supine position before ECGs are taken. Obtain ECGs and blood samples for serum hormones, to the best of the site and participants' ability, at approximately the same time of day (preferably in the morning) at each indicated visit to minimize diurnal variation. Record the time of collection. Additional ECG assessments may be performed at any time during trial participation if clinically indicated.

q MK-6240 tau PET scan should be scheduled as soon as possible. Due to the potential for scheduling challenges for MK-6240 tau PET, or in the event of tracer failure, randomization may be delayed, and the screening period extended by 14 days and the Week 24 deviation window may be extended up to +21 days, with Sponsor Medical Monitor approval, though effort should be made to schedule it as close as possible to each indicated timepoint. The Day 1 visit MK-6240 tau PET scan may be performed once a subject is deemed eligible for randomization but no earlier than 21 days before randomization. At the Day 1 visit, participants must have completed the MK-6240 tau PET scan prior to randomization.

r The screening brain MRI scan may be used as the baseline volumetric MRI scan for a participant.

Table 3 Schedule of Activities: Long-term Extension Period

Visit:	Week 24[a,b]	Week 26	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 54	Week 60	ET[c]	FU[d]
Visit Window (Days):	±7	-4	±7	±7	±7	±7	±7	±7	±7	±7	±7	4 weeks (+14 days) post last dose
Contact IWRS	X[e]							X	X	X	X	
Physical Examination (including neurological) and Weight	See Table 2							X		X	X	
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Dispense/Review ASN51 Compliance[f]			X	X	X	X	X	X	X	X	X	
Efficacy Measures												
ADAS-Cog13[g]					X			X		X	X	
CDR-SB[g]					X			X		X	X	
MMSE[g]					X			X		X	X	
Safety Assessment												
Adverse Events[h]		X	X	X	X	X	X	X	X	X	X	X
C-SSRS[i]		X	X	X	X	X	X	X	X	X	X	X
Laboratory Specimens[j]												
Clinical chemistry, hematology[k]		X	X	X	X	X	X	X	X	X	X	X
Coagulation panel									X		X	
Urinalysis					X			X		X	X	
Serum hormone markers[k]					X			X		X	X	
Plasma for biomarker storage[l]			X		X			X		X	X	
Plasma for ASN51[k]											X	
Optional CSF for biomarker storage[k,l]										X	X	
Other Safety Measures												
Vital signs[m]		X	X	X	X	X	X	X	X	X	X	(X)
ECG in triplicate[n]		X	X	X	X	X	X	X	X	X	X	(X)
Imaging Assessments												
Brain MRI[o]										X	X	
18F MK-6240 PET scan[p]										X	X	

AD = Alzheimer's disease; ADAS-Cog13 = Alzheimer's Disease Assessment Scale – Cognitive Behavior Subscale 13; AE = adverse event; CDR-SB = Clinical Dementia Rating – Sum of Boxes; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; EU = European Union; FSH = follicle-stimulating hormone; FU = follow-up; HBsAg = Hepatitis B virus surface antigen; IVDR = in vitro diagnostic regulation; IWRS = interactive web response system; LTE = Long-term Extension; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics.

Consult Section 8 for guidelines on procedures and assessments. Consult the Study Reference Manual for additional information, including a recommended order of (specific) assessments for each visit.

a Participants enrolled in the LTE Period will be dispensed study intervention at the Week 24 visit. No Week 24 assessments should be repeated from the main study.

b Schedule all remaining visits at Week 24 visit. Visits may take more than 1 day but should take place as close to the target date as possible.

c Early termination eCRFs should be completed if a participant discontinues before the Week 60 Visit. Schedule FU visit 4 weeks after the last dose of ASN51.

d Schedule the FU visit 4 weeks after the last dose of ASN51 for safety assessment. The FU visit may be conducted by phone, however, any participant with an ongoing AE, or history of abnormal ECGs should be monitored by the Investigator and managed appropriately (with an in-clinic visit, including vital signs and ECG, if necessary).

e ASN51 should be taken once daily in the morning with or without food. The first dose should be taken at the clinic visit under supervision.

f Participants should be instructed to bring all study medication to the site at each indicated visit to assess compliance. If an EY visit, no study intervention (ASN51) should be dispensed.

g Whenever performed on the same day, cognitive and functional assessments (ADAS-Cog13, CDR-SB, and MMSE) are to be performed before procedures that may be stressful for participants (for example, MRI, PET, blood draw, or CSF sampling).

h Any clinically significant changes from baseline in the physical examination should be noted as an AE.

i The "Since Last Visit" questionnaire will be administered at all subsequent visits.

j Unscheduled laboratory tests may be performed at any time at the discretion of the Investigator if clinically indicated for a suspected adverse event.

k Record date and times of sample collection on the Lab Requisition Form, for all PK samples, record the date and time of most recent ASN51 dose and whether participant is in fed or fasted state.

l Blood and CSF for biomarker storage and are to be collected unless collection and/or transportation of the sample is prohibited due to local regulations.

m Obtain vital signs while participant has been in a seated position for at least 5 minutes.

n ECGs should be taken in triplicate at approximately 1-minute intervals. Participants should rest for at least 5 minutes in the supine position before ECGs are taken. Obtain ECGs, to the best of the site and participants' ability, at approximately the same time of day at each visit to minimize diurnal variation. Additional ECG assessments may be performed at any time during trial participation if clinically indicated.

o Perform MRI after any cognitive and functional assessments. Alternatively, MRI may be performed at least 1 day before cognitive and functional assessments. Volumetric MRI will be performed.

p Due to the potential for scheduling challenges for MK-6240 tau PET, or in the event of tracer failure, the deviation window may be extended to +21 days of the indicated visits.

2 INTRODUCTION

2.1 Purpose of Trial

ASN51 is a reversible and substrate competitive inhibitor of O-linked [redacted] N-acetylglucosaminidase (O-GlcNAcase; OGA), which is in clinical development for the treatment of AD caused by intracellular brain proteinopathies.

In patients with AD, the formation of neurofibrillary tangles (NFTs) consisting of the protein tau is tightly linked to the onset and progression of dementia symptoms (La Joie, Visani et al. 2020). Inhibition of the OGA enzyme with ASN51 stabilizes a post-translational carbohydrate modification of tau called O-GlcNAc by preventing its removal. Increasing the level of O-GlcNAc modification of tau is hypothesized to prevent the aggregation of tau into toxic paired helical filaments that deposit as NFTs in the brains of patients with AD. Orally administered OGA inhibitors have been shown to slow the development of NFT pathology in preclinical models of early AD by up to 80% in some brain regions and represent a promising new disease-modifying treatment approach (Yuzwa, Shan et al. 2012, Graham, Gray et al. 2014, Yuzwa, Shan et al. 2014, Hastings, Wang et al. 2017, Wang, Smith et al. 2018, Wang, Li et al. 2020, Permanne, Sand et al. 2022, Pratt and Vocadlo 2023, Rostgaard, Jul et al. 2023, Mergott 2024, Nery 2024).

ASN51 has been administered to healthy volunteers in multiple Phase 1 clinical trials to date and has been deemed suitable for chronic dosing in this Phase 2 study of early AD based on available nonclinical and clinical data as described in the Investigator's Brochure (IB).

The purpose of the ASN51-201 trial is to evaluate the safety, pharmacokinetics (PK), effect on biomarkers of disease pathophysiology and pathology, and preliminary effects on measures of clinical efficacy of multiple doses of ASN51 in adults with early, symptomatic AD.

2.2 Summary of Benefits and Risks

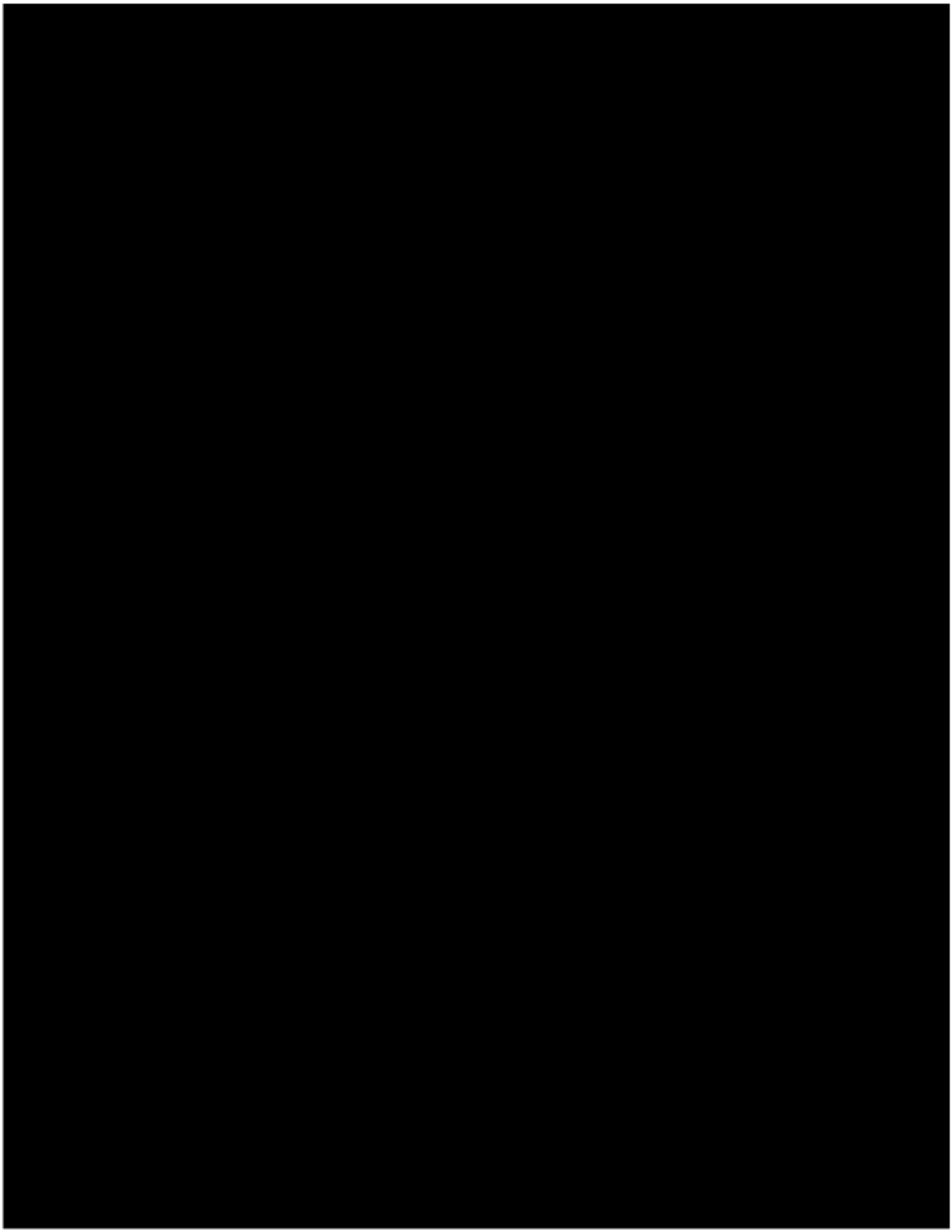
[redacted]

[redacted]

2.2.2 Risk Summary

2.2.2.1 Intervention Risks and Mitigation

[redacted]



[redacted]

2.2.3 Overall Benefit: Risk Conclusion

[redacted]

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of daily doses of ASN51 as compared with placebo	• Incidence and severity of AEs • Changes from baseline in laboratory safety assessments (including clinical chemistry, hematology, urinalysis, and serum hormone markers), • Changes from baseline in vital signs, 12-lead electrocardiograms, and physical (including neurological) examinations • Changes from baseline in C-SSRS
Key Secondary	
To evaluate the effect of daily doses of ASN51 as compared with placebo on the pathophysiology of early AD To evaluate the effect of ASN51 versus placebo in change from Baseline to Week 24 on the pathophysiology of early AD	• Change from baseline through Week 24 in CSF pTau217 • Change from baseline through Week 24 in CSF total tau protein • Change from baseline through Week 24 in plasma pTau217
Other Secondary	
To evaluate the effect of daily doses of ASN51 as compared with placebo on tau pathology in early AD	Change from baseline through Week 24 in MK-6240 tau PET signal
To evaluate the pharmacokinetics of ASN51 in early AD	Trough (C_{min}) at steady state and maximum (C_{max}) concentration of ASN51 in plasma at steady state through Week 24
Tertiary/Exploratory	
To evaluate the effect of daily doses of ASN51 as compared with placebo on the pathophysiology of early AD To evaluate the effect of ASN51 versus placebo in change from Baseline to Week 24 on biomarkers of early AD	Change from baseline through Week 24 in biomarkers, including but not limited to: Plasma • Phosphorylated tau 181, GFAP, Aβ42/40, NFL CSF • Phosphorylated tau 181, microtubule binding region tau 243, GFAP, Aβ42/40, NFL, neurogranin

To evaluate the effect of daily doses of ASN51 as compared with placebo on clinical progression in early AD	Change from baseline through Week 24 in: • CDR-SB score • ADAS-Cog13 score • MMSE score • ADCOMS score
To evaluate the efficacy of ASN51 versus placebo in change from Baseline to Week 24 on brain structure	Change from baseline through Week 24 in volumetric brain MRI parameters (e.g., whole brain volume, lateral ventricular volume, and cortical thickness measures of certain brain regions)
Extension Period	
To evaluate the long-term safety and tolerability of ASN51 in early AD	The incidence and severity of AEs over the DB placebo-controlled and LTE periods of the study
To evaluate the long-term efficacy of ASN51 as measured by clinical, radiological, and additional assessments reported by the participant and study partner	Change over the placebo-controlled (from DB baseline) and long-term extension (from LTE baseline) periods of the study in: • Disease-related biomarker levels in CSF, which will include, but are not limited to, amyloid and tau proteins (in a subset of participants) • Disease-related biomarker levels in blood, which will include, but are not limited to, amyloid and tau proteins • MK-6240 tau PET signal • Whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI • CDR-SB score • ADAS-Cog13 score • MMSE score • ADCOMS score

AD = Alzheimer's disease; ADAS-Cog13 score = Alzheimer's Disease Assessment Scale – Cognitive Behavior Subscale 13; ADCOMS = Alzheimer's disease composite score; AE = adverse event; CDR-SB = Clinical Dementia Rating – Sum of Boxes; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; DB = double-blind; GFAP = glial fibrillary acidic protein; LTE = Long-term Extension; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NFL = neurofilament light chain; PET = positron emission tomography.

4 TRIAL DESIGN

4.1 Description

ASN51-201 is a multi-site, placebo-controlled, double-blind, randomized, parallel group trial with a long-term extension (LTE). The purpose of the trial is to evaluate the safety, PK, effect on biomarkers of disease pathophysiology and pathology, and preliminary effects on measures of clinical efficacy of multiple doses of ASN51 in adults with early AD.

The trial design is depicted in Section 1.2.

Screening for eligibility will be conducted using a tiered approach and may be completed over multiple days. An abbreviated screening informed consent process may be utilized to conduct initial prescreening (i.e., denoted Tier 1 and Tier 2 per Table 1), if allowed at the investigative site. Participants who meet Tier 1 eligibility criteria, including MMSE, should proceed to Tier 2 (plasma pTau217). Tier 1 and Tier 2 assessments may take place on the same day.

Informed consent for the full trial must be obtained prior to performing any Tier 3 and Tier 4 screening procedures 2 per Table 1. Participants may proceed to Tier 4 only after all criteria from Tier 1, 2, and 3 have been met.

The duration of the Screening Period may be up to 8 weeks (may be extended on a case-by-case basis by the Sponsor Medial Monitor) to allow for the completion of assessments and for the evaluation of required laboratory, ECG, and imaging tests per the Schedule of Activities provided in Table 1.

Dose selection has been enabled by two Phase 1 target engagement trials that utilized an OGA enzyme PET ligand to define the precise relationship in human beings between plasma concentration and brain target occupancy. Further details on dose selection can be found in Section 6.2.

Eligible participants will be randomized in a 1:1:1 ratio to one of the following planned arms:

- ASN51: [redacted] once daily by mouth
- ASN51: [redacted] once daily by mouth
- Placebo once daily by mouth.

Eligible participants will self-administer ASN51 once daily at the assigned dose level during a 24-week Double-blind (DB) Intervention Period. The participant (accompanied by a designated study partner) will be asked to return to the investigative site approximately every 4 weeks over two days as long as all assessments are completed within the visit window.

Following completion of the DB Intervention Period, all participants will be offered continued ASN51 in the 36-week LTE Period. Participants initially randomized to placebo will receive ASN51 (randomized 1:1 [redacted]) during the LTE Period. Participants randomized to

ASN51 will continue at the assigned dose level, unless dose modification is recommended based on emerging data.

A safety Follow-up Visit will take place 4 weeks after the last dose of ASN51.

A Schedule of Activities for the DB Intervention Period and LTE Period are provided in Table 2 and Table 3, respectively.

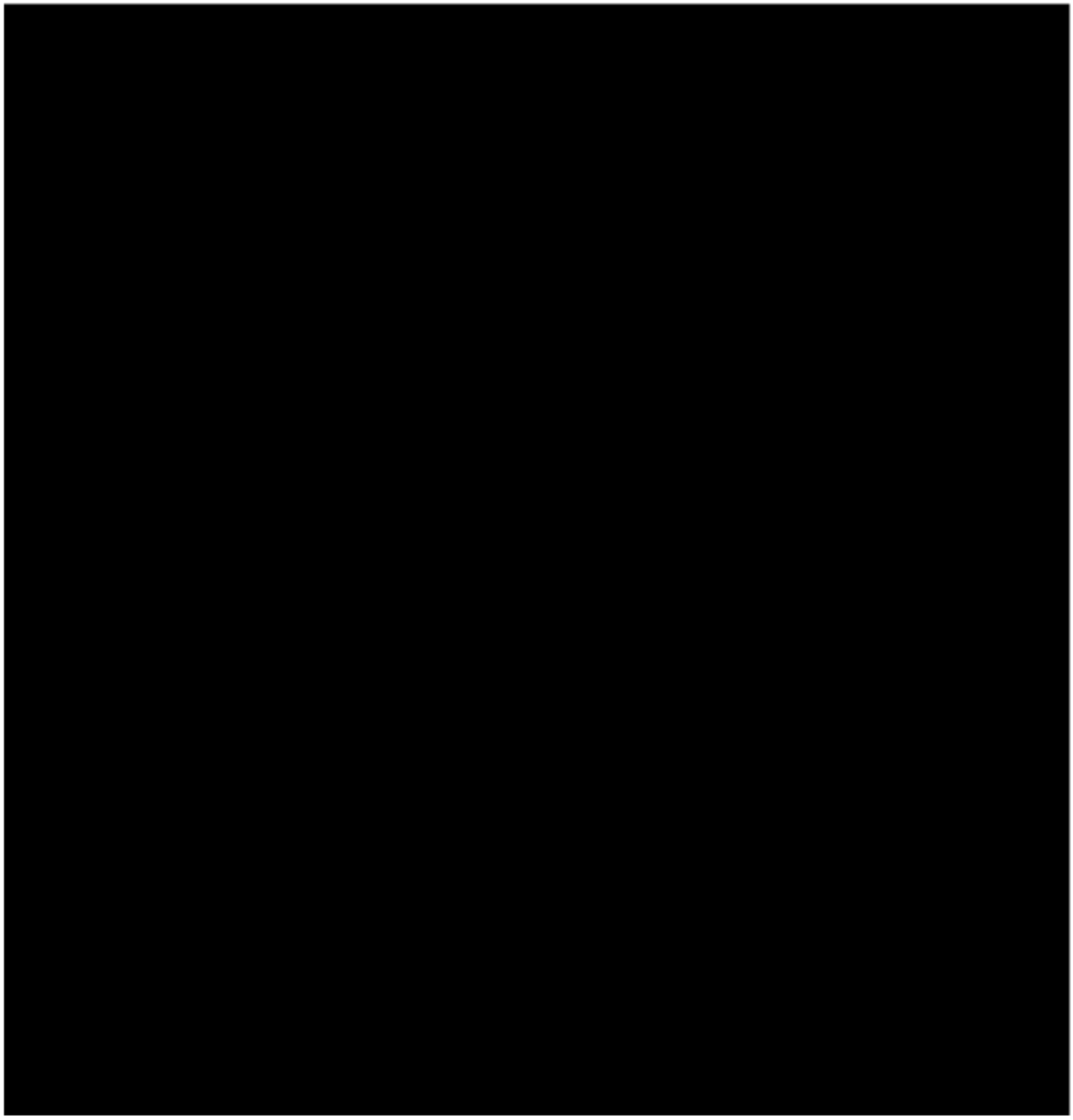
4.2 Rationale for Trial Design

ASN51-201 is the first trial to investigate the safety, tolerability, PK, effect on biomarkers of pathology and pathophysiology, and exploratory effect on measures of cognition and function of ASN51 in adults with early AD. [redacted]

The 24-week DB Intervention Period of chronic administration of ASN51 in patients with early AD is appropriate to establish safety and tolerability of ASN51 at multiple dose levels as measured by changes in laboratory safety assessments (including clinical chemistry, hematology, urinalysis, and serum hormone markers), vital signs, 12-lead ECGs, Columbia-Suicide Severity Rating Scale (C-SSRS), and physical examinations (including neurological examination).

The 24-week DB Intervention Period is also of sufficient duration to perform a population PK analysis of trough (C_{min}) and peak (C_{max}) PK at steady-state, to observe initial changes in AD pathophysiology and pathology as measured by fluid biomarkers, and to observe initial changes in cognitive function as assessed by AD clinical outcome measures.

[redacted]



4.3 Start of Trial and End of Trial

The Start of the Trial is the estimated date on which the clinical trial will be open for recruitment of participants.

A participant will be considered enrolled in the trial once all screening procedures have been completed, the results evaluated by the Investigator to confirm eligibility, and the participant is randomized into the trial.

The end of the trial is defined as the date of the last protocol-specified visit for the last participant participating in the trial.

The Sponsor reserves the right to discontinue the trial at any time for any reason or discontinue participation of an investigator due to poor enrollment or noncompliance (Section 10.5).

5 POPULATION

5.1 Selection of Trial Population

This trial will be conducted in adults (aged 50 to 80 years) with a diagnosis of early AD. Eligible patients should meet diagnostic criteria for mild cognitive impairment (MCI) due to AD or mild AD dimentia, collectively referred to as early AD. All patients should have a plasma pTau217 concentration above a pre-determined cut-off to confirm the presence of brain amyloid pathology. Mini Mental Status Examination (MMSE) should range between ≥ 20 and ≤ 28 at baseline with a global Clinical Dementia Rating (CDR) score of 0.5 or 1.0. All participants should meet National Institute on Aging and the Alzheimer's Association (NIA-AA) diagnostic criteria for MCI or mild AD (Jack, Bennett et al. 2018) and have a CDR memory box score of 0.5 confirming episodic memory impairment.

5.2 Rationale for Trial Population

Early AD patients are expected to have tau pathology present at baseline, maximizing the probability of observing an anti-tau treatment effect with ASN51.

The Sponsor has taken reasonable measures to ensure the protection and safety of this population including specific criteria to exclude patients with significant cardiovascular or neurological conditions, or who require concomitant medications for conditions which may confound trial results. Additional criteria related to concomitant medications or abnormal coagulation parameters were included to mitigate risks associated with LP procedures. Considerations included comorbidities likely present in the selected population, and emerging safety data from Phase 1 clinical trials.

For Investigator questions regarding participant eligibility or clinical significance of abnormalities, discussion with the study Medical Monitor is strongly encouraged.

Individuals who do not meet criteria for trial eligibility must not be enrolled; there will be no protocol waivers or exemptions.

5.3 Inclusion Criteria

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Male or female age 50 to 80 years inclusive at the time of consent.
2. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian, where local regulations and institutional practices permit), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.

3. Must consent to APOE genotyping. The participant's APOE status may be disclosed to him/her at the Investigator's discretion.
4. Must have a care partner who, in the Investigator's judgment, has frequent and sufficient contact with the participant (at least 10 hours/week) as to be able to provide accurate information about the participant's cognitive and functional abilities. The care partner must agree to accompany the participant to clinic visits and/or be available by telephone at designated times to provide information to the Investigator and study staff about the participant (and to attend in-person clinic visits that require care partner input for scale completion) and must agree to monitor the participant's administration of any prescribed medications. A care partner should be available for the duration of the study, and the participation of the same care partner for the duration of the study is a top priority. The care partner must be literate and provide informed consent.
5. A plasma pTau217 result consistent with the presence of amyloid pathology (defined as > 0.18 pg/mL).
6. A clinical diagnosis of AD at either the mild cognitive impairment or mild AD dementia stage per NIA-AA criteria (Jack, Bennett et al. 2018), consistent with Stage 3 and Stage 4 in the FDA draft guidance for early AD (FDA draft 2024).
7. Gradual and progressive change in cognition for at least 6 months as reported by the participant and study partner.
8. Global CDR of 0.5 to 1 (inclusive) and memory box score ≥ 0.5 at Screening.
9. MMSE score of 20 to 28 (inclusive).
10. Body mass index greater than 18.5 and less than 35 at Screening.
11. All men, regardless of fertility status, with non-pregnant women of childbearing potential partners must agree to at least one of the following contraception requirements from 28 days before baseline assessment through 90 days after last study drug administration:
    a. Total abstinence: if in line with their preferred and usual lifestyle
    b. Male sterilization by vasectomy with documentation of the procedure
    c. Condom use
    d. A highly effective method of contraception (Section 13.1.2) for the partner of a male participant.
12. Apart from a clinical diagnosis of MCI due to AD or mild AD dementia, the participant must be in good health as determined by the Investigator, based on medical history and screening assessments.

5.4 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this trial:

5.4.1 Exclusion Criteria by Medical History

1. Any medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause to the participant's cognitive impairment (e.g., current history of substance abuse, uncontrolled vitamin B12 deficiency or abnormal thyroid function, stroke or other cerebrovascular condition, normal pressure hydrocephalus, Parkinson's disease, Lewy body dementia, cerebral amyloid angiopathy, frontotemporal dementia) or could lead to discontinuation, lack of compliance, interference with study assessments, or safety concerns.
2. Non-amnestic presentation of AD as judged by the Investigator.
3. Woman of childbearing potential (per CTFG 2020).
4. Excessive alcohol use (defined as more than 3 alcoholic drinks per day or 21 drinks per week for men and 2 alcoholic drinks per day or 14 drinks per week for women) from the Screening Visit until the end of the Follow-up Period.
5. History of cancer in the past 3 years. *Exceptions:* non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, non-progressive prostate cancer, participants with cancer in remission > 5 years, or other cancers with low risk of recurrence or spread.
6. History of human immunodeficiency virus infection (active or past), or active hepatitis C infection.
7. History of liver disease including hepatitis B, hepatitis C, primary biliary cholangitis, primary sclerosing cholangitis, alpha-1 antitrypsin disease, alcoholic liver disease, Wilson's disease, hemochromatosis, portal hypertension, biopsy-proven metabolic associated steatohepatitis, autoimmune hepatitis, drug induced liver disease.
8. Clinically significant systemic infection or severe infection (e.g., pneumonia, septicemia) within the 30 days prior to Screening or between Screening and Day -1.
9. History of seizures within 10 years prior to Screening Visit 1 or history of epilepsy (except for history of febrile seizures in childhood).
10. Presence of clinically significant and/or unstable psychiatric illness, in the Investigator's opinion (e.g., bipolar disorder), within the 6 months prior to Screening Visit 1 and/or a documented prior history of chronic schizophrenia.
11. History of major depressive disorder, bipolar disorder, or generalized anxiety disorder with an active episode in the past 5 years.

12. History of diabetes mellitus. Participants with well-controlled diabetes mellitus and a hemoglobin A1c < 7% are permitted.
13. Biotin supplementation ≥ 5,000 mcg/day from 28 days prior to Screening through the end of the Follow-up Period
14. History of bleeding disorder or predisposing conditions, blood clotting, or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
15. Any major surgery within 12 weeks of Screening Visit 1 or during the screening period.
16. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to Screening Visit 1.
17. Uncontrolled hypertension defined as an average of 3 systolic/diastolic blood pressure readings > 165 mmHg and/or > 100 mmHg, respectively, at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the participant to be eligible for the study) or persistent systolic/diastolic blood pressure readings > 180/100 mmHg within 12 weeks prior to randomization (Study Day 1) that, in the opinion of the Investigator, are indicative of chronic uncontrolled hypertension.
18. History of severe allergic or anaphylactic reactions.
19. Known or suspected history of drug or alcohol abuse within 2 years prior to Screening. Benzodiazepine and opioid use is permitted if in the clinical opinion of the Investigator the use is for an appropriate medical condition and not due to drug abuse.
20. Current serious or unstable illness, or any other condition that, in the judgement of the Investigator, would interfere with the ability to complete the study, pose significant risk to participant safety, or potentially confound interpretation of trial results.

5.4.2 Exclusion Criteria by Screening Assessments

21. Any clinically significant abnormality at screening in physical examination, vital signs, ECG, or laboratory test results that could place the participant at undue risk during the study, compromise the future interpretation of study assessments, or that suggests an alternative etiology for dementia other than AD.
22. At risk of suicide based on a "yes" response to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation question 4 or 5 or any suicidal behavior assessment within 6 months before Screening, or has been hospitalized or treated for suicidal behavior within 5 years of Screening.

23. Magnetic resonance imaging (MRI) evidence of vascular dementia or other findings suggestive of a major neurologic disorder other than AD.
24. Significant claustrophobia during MRI that, in the opinion of the Investigator, will prevent successful completion of required procedures.
25. Heart rate > 100 beats per minute after 5 minutes of rest, without solicitation.
26. Confirmed demonstration of corrected QT interval using Fridericia's correction method (QTcF) of > 450 ms for males and > 460 ms for females (as read by the central reading facility).
27. Median ECG (triplicate) PR interval > 200 msec at Screening.
28. Positive hepatitis B virus surface antigen and/or hepatitis B e-antigen at Screening.
29. Positive hepatitis C antibody test result at Screening.
30. Presence of bleeding disorder or abnormal coagulation parameters at Screening, including platelet count < 150,000 cells/µL or international normalized ratio (INR) > 1.5.
31. Estimated glomerular filtration rate < 60 mL/min/ 1.73 m^2 per Chronic Kidney Disease Epidemiology Collaboration at Screening.
32. Liver function, any of the following: ALT ≥ 1× the ULN, AST ≥ 1× ULN, total bilirubin level (TBL) ≥ 1× ULN, or alkaline phosphatase (ALP) ≥ 1× ULN at screening. Subjects with any degree of hepatic impairment as defined by the Child-Pugh classification are also excluded (e.g., classification B or C).

5.4.3 Exclusion Criteria by Concomitant Medications/Prior Therapies

33. Initiation or change in dose of an acetylcholinesterase inhibitor and/or memantine within less than 8 weeks prior to randomization.
34. Positive urine drug test at Screening. Testing positive for benzodiazepines or opioids in urine drug testing is permitted if determined by the Investigator to be due to appropriate medical use and not drug abuse. Medical cannabidiol (CBD) use is permitted if prescribed by a medical provider in accordance with local laws and if in the opinion of the Investigator its use does not pose a risk to participant safety or compromise a participant's performance on cognitive assessments.
35. Taking medications known to prolong PR or QT intervals (e.g., calcium channel blockers or beta blockers) unless on a stable dose of (or titrating) within 12 weeks prior to randomization.
36. Use of any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the participant at higher risk for AEs, or impair the participant's ability to perform cognitive testing or complete study procedures.

37. Any prior or ongoing exposure to active or passive anti-amyloid immunotherapy, anti-tau immunotherapy, an anti-tau antisense oligonucleotide or gene therapy, or O-GlcNAcase inhibitor.
38. If previously exposed to an investigational product other than active or passive anti-amyloid immunotherapy, anti-tau immunotherapy, an anti-tau antisense oligonucleotide or gene therapy, or O-GlcNAcase inhibitor, then 12 weeks or 5 half-lives (whichever is longer) must have passed prior to randomization.
39. Known allergy to any components of the ASN51 formulation.
40. Requires use of anticoagulants during trial participation (to permit safe CSF collection).
41. Prior use of a moderate or strong inhibitor of CYP3A4 within a period of 5 half-lives of randomization (refer to Appendix 16).
42. Prior use of a moderate or strong inhibitor of CYP2C19 within a period of 5 half-lives of randomization (refer to Appendix 16).

5.4.4 Procedural Exclusions

43. Unable to swallow [redacted] capsules once daily.
44. Known sensitivity to 18F-MK-6240.
45. Poor venous access.
46. Has any of the following contraindications to having a LP, including, but not limited to:

- Screening values of platelet count and coagulation parameters including INR, prothrombin time, and partial thromboplastin time or other coagulopathy should be within normal ranges. Participants with nonclinically significant and stable out-of-range values may be eligible to enroll in the study at the discretion of the Investigator.
- Administration of any antiplatelet or anticoagulant medication (e.g., aspirin [unless ≤ 325 mg/day], clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban) that cannot be safely held before and/or after an LP procedure according to local or institutional guidelines and/or Investigator determination.
- Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that is not managed optimally and could place a participant at an increased risk for procedural bleeding. These could include, but are not limited to, known anatomical factors at or near the LP site (e.g., vascular abnormalities, neoplasms, or other abnormalities).
- Lumbar spine deformity and/or known evidence on MRI contraindicating LP.
- Clinical signs or symptoms detected during neurological exam (e.g., focal neurological signs, altered mental status, papilledema) or radiographic evidence (e.g., enlarged ventricles, herniation, or mass effect) of increased intracranial pressure.

Any symptoms caused by or related to the LP if performed during Screening must be resolved prior to randomization.

47. Contraindication to MRI.
48. Contraindication to having a PET scan (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET radioligand, imaging agent, or any of the excipients; failure to participate in and comply with previous PET scans).
49. Planned or recent exposure to ionizing radiation that when combined with study PET imaging procedures would result in a cumulative exposure to radiation that exceeds local limits.

5.4.5 Other Exclusions

50. Participant living in an organized care facility with extensive intervention and/or support of daily living activities (e.g., a nursing home).
51. Blood donation (1 unit or more) within 90 days prior to Screening Visit 1, plasma donation from 1 week prior to Screening Visit 1, and platelet donation from 6 weeks prior to Screening Visit 1.
52. Inability to comply with study requirements.
53. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the participant unsuitable for enrollment.

5.5 Lifestyle Considerations

5.5.1 Meals and Dietary Restrictions

No restrictions.

5.5.2 Physical Activity

No restrictions.

5.5.3 Other Activity

Participants must refrain from donating blood or blood products from the screening visit until 1 month after the last dose of ASN51.

Male participants should refrain from sperm donation from the screening visit until 90 days after the last dose of ASN51.

5.6 Screen Failures

Prospective participants will be evaluated for eligibility per inclusion and exclusion criteria (Sections 5.3 and 5.4) as detailed in Section 8.1 and Table 1.

An individual who does not meet any inclusion criteria or meets one or more exclusion criteria will be deemed ineligible; the reason for screen failure will be documented. No exceptions to eligibility criteria (i.e., protocol waivers) will be granted.

Rescreening may be considered in consultation with the Medical Monitor if there is a change in the individual's status. Rescreening is not allowed if the reason for screen failure is an imaging test for AD or biomarker unless due to technical issue with sample or processing. An abnormal laboratory test result may be repeated once within the screening period without the participant being considered a rescreen.

6 INTERVENTIONS AND CONCOMITANT THERAPY

Site staff should follow the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. Study treatment are for one-time use only; do not use any study treatment remaining in the vial for another participant.

6.1 Description of Trial Intervention

Eligible participants will be randomized in a 1:1:1 ratio to receive ASN51 [redacted], ASN51 [redacted], or placebo. To maintain the blind, all participants will take a total of 4 capsules by mouth once a day as summarized in Table 4.

Table 4 Trial Interventions: Daily Dose Administration

Randomized Assignment	Number of ASN51 Capsules [redacted]	Number of Matched Placebo Capsules	Total Capsules Administered (orally, once daily)
ASN[redacted]	2	2	4
ASN[redacted]	4	0	4
Placebo	0	4	4

6.1.1 Investigational Medicinal Product: ASN51

The investigational medicinal product (IMP), ASN51, is a reversible and substrate competitive small molecule inhibitor of O-GlcNAcase. ASN51 drug product formulation is supplied in capsule form at [redacted] free base equivalent dosage strength. ASN51 is intended for oral administration.

The IMP is manufactured, packaged, and labeled according to current Good Manufacturing Practice regulations.

6.1.2 Control/Comparator: Placebo

Placebo capsules (equivalent to [redacted] ASN51) will be matched in color, shape, size, and number of capsules. Placebo capsules will serve as a control for the DB Intervention Period, and to maintain the blind for participants assigned to receive ASN51 [redacted].

No active comparator or any other additional drug products will be provided as part of the trial.

6.2 Rationale for Trial Intervention

6.3 Dosing and Administration

All participants will take a total of [redacted] ASN51 and/or placebo capsules once daily to achieve the assigned dose level and maintain the blind.

Participants will be provided with dosing instructions; capsules will be taken orally, with or without food, and should be administered approximately the same time each day, preferably in the morning.

For any dose not taken within 12 hours (± 2 hours) of the usual time, or within 12 hours (± 2 hours) of prior dose participants will be instructed to withhold dosing on that day. Participants will be instructed not to make up the missed doses.

If drug-related tolerability issues are suspected for an individual participant, contact the Sponsor Medical Monitor for guidance.

6.4 Treatment of Overdose

No antidotes or antagonists exist for the treatment of a potential ASN51 overdose. Clinical symptoms will be treated as deemed appropriate by the Investigator and/or treating physician.

All AEs associated with overdose should be documented in the electronic case report form (eCRF) and reported following procedures for the reporting of Serious Adverse Events (Section 12.3).

6.5 Preparation, Handling, Storage, and Accountability

6.5.1 Preparation of Trial Intervention

ASN51 will be supplied in capsule form and dispensed to the participant.

During the DB Intervention Period, matched placebo will be supplied in capsule form and dispensed to the participant as assigned.

6.5.2 Handling and Storage of Trial Intervention

At the investigative site, IMP must be securely stored under conditions indicated in the IB; IMP accountability is the responsibility of the Investigator (Section 10.5).

Details on handling and storage of ASN51 (placebo) capsules are provided in the Study Reference Manual.

6.5.3 Accountability of Trial Intervention

The Investigator is responsible for ensuring IMP is stored in a secure limited access location at controlled temperature as described in the IB and according to product packaging. The storage facility must be available for inspection by the trial monitor at any time during the trial.

A drug accountability record must be maintained for all IMP received, dispensed, returned, and/or lost during the trial. This record must be kept current and made available to the trial monitor for inspection. Following the close-out of the trial, all unused IMP must be returned to Sponsor and/or its designee unless other instructions have been provided for final disposition of the IMP.

6.6 Participant Assignment, Randomization, and Blinding

6.6.1 Participant Assignment

Participants will be sequentially assigned an identification number upon signing of informed consent.

Once eligibility is confirmed, participants will be randomized via an Interactive Web Response System (IWRS). Randomization will be stratified as described in Section 4.2.

6.6.2 Blinding and Unblinding

The initial 24 weeks of intervention will be administered in a double-blind fashion. Participants, Investigators, site personnel, and the Sponsor and/or designees will be blinded to randomization assignment.

The statistician(s) responsible for generating the randomization schedule, and personnel responsible for preparing trial intervention supplies will be unblinded.

Randomization numbers will be assigned sequentially. Each participant will be dispensed blinded trial intervention (ASN51 or placebo), labeled with the participant's unique randomization number. Unblinding mechanisms will be available by IWRS.

Should any trial stopping criteria (Section 7.4) be triggered the involved participant(s) will be unblinded to randomization assignment by the SRC to determine if the event was related to IMP.

In the event of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's randomization assignment is warranted. The safety of the participant will be the first consideration in making such a determination. If a participant's randomization assignment is unblinded, the Sponsor Medical Monitor must be notified within 24 hours.

Following completion of the 24-week DB Intervention Period, data will be unblinded after database lock for the purpose of data analysis; however, participants, Investigators, and study site staff will remain blinded to DB treatment assignment until the end of the 36-week LTE Period (end of the study).

6.6.3 Randomization

Participants will be randomized (1:1:1) to ASN51 at 1 of 2 dose levels, or placebo.

The randomization schedule will be computer generated by the Sponsor or designee. An IWRS will be used.

6.7 Trial Intervention Compliance

Site personnel will maintain a record of all IMP dispensed to each participant. Participants will also be instructed to bring all IMP containers (blister packs and/or unused capsules) to each clinic visit.

6.8 Concomitant Therapy

Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except those specified as prohibited medications (Section 6.8.1).

6.8.1 Prohibited Concomitant Therapy

To be eligible for the trial, participants must not require chronic daily drug intake of the medications listed below. If participants discontinue any of these medications prior to randomization, a washout period of the lesser of 5 half-lives or 30 days is required.

The following medications will remain prohibited throughout the DB Intervention Period:

- Any investigational product intended for AD (e.g., anti-tau antisense oligonucleotide or gene therapy, active or passive anti-amyloid immunotherapy, active or passive anti-tau immunotherapy, O-GlcNAcase inhibitor, etc.) or other investigational product within 8 weeks prior to randomization
- Anticoagulants
- Moderate and strong inhibitors of CYP3A4 and CYP2C19 (refer to Appendix 16).

During the LTE Period, use of prohibited/restricted medications will be addressed on a case-by-case basis in consultation with the Sponsor Medical Monitor.

6.8.2 Permitted Concomitant Therapy

Concomitant therapy, particularly medications that could potentially affect cognition, should be maintained at stable doses throughout the trial, unless a change is medically necessary.

Medications (investigational, prescription, over the counter, and herbal) and nutritional supplements taken during the 30 days prior to Day 1 will be reviewed and recorded as prior medications.

All concomitant medications taken during the trial, and any changes since the previous visit, will be recorded. Dose, route, unit frequency of administration, indication, and date(s) of administration will be captured.

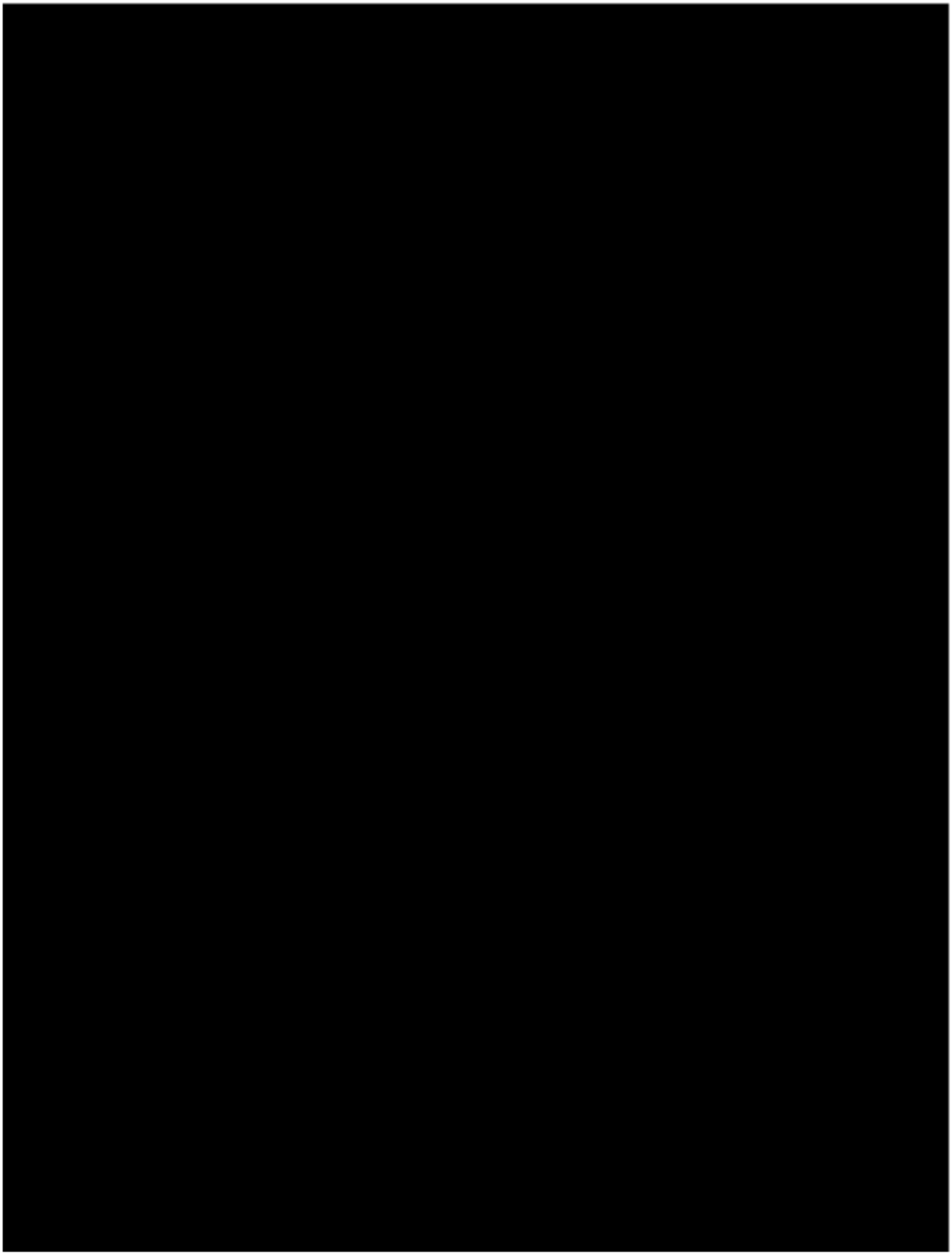
If participant is taking high dose biotin supplements (biotin ≥ 5,000 µg/day, found in multivitamins, biotin supplements, and supplements for hair, skin, and nail growth), a washout of 1 week before randomization is permitted.

6.8.3 Rescue Therapy

Not applicable.

6.8.4 Additional Protocol-designated Products – Positron Emission Tomography Imaging Radioligands

[redacted]



7 DISCONTINUATION OF INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Trial Intervention

7.1.1 Criteria for Permanent Discontinuation of Trial Intervention

The Investigator and Sponsor have the right to remove participants from the trial. The Sponsor also reserves the right to discontinue participation of an individual participant.

Clinical judgement

Trial intervention may be discontinued, and participants may be removed from the trial for the following reasons:

- Occurrence of an AE or SAE that precludes further participation
- Any condition that, in the judgment of the Investigator or Sponsor, might place the participant at risk or invalidate the trial
- At the request of the participant, Investigator, or Sponsor, for administrative or other reasons
- Protocol deviation or noncompliance.

Hepatic event or liver test abnormality

Participants who are discontinued from IMP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected and recorded in the eCRF as deemed necessary by Investigator to accurately follow event until resolution or baseline return.

Discontinuation of IMP for a liver test abnormality should occur when a participant meets any of the following conditions:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP > 3 × ULN
- ALP > 2.5 × ULN and TBL > 2 × ULN
- ALP > 2.5 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

C-SSRS

In addition, IMP may be discontinued if participants:

- Answer "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or
- Answer "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist may assist in the decision to discontinue the participant.

ECG

If a clinically significant finding is identified (including changes from baseline in QTcF) after enrollment, the Investigator or qualified designee will determine if the participant may continue in the trial or if a change in participant management is required. Review of ECGs must be documented upon collection and any new clinically significant ECG finding should be reported as an AE. Central review of ECGs will also be performed (see Section 8.3.3.1).

Should the following events occur in an individual participant during the trial, the Investigator, in consultation with the Sponsor's Medical Monitor, will decide if study intervention should be interrupted or permanently discontinued:

- If a participant has median PR interval of 200 ms to 220 ms *AND* a change from baseline in PR interval of > 10% (triplicate measurements)
- If a participant has median PR interval > 220 ms (triplicate measurements).

Systemic Hypersensitivity Reactions

If the Investigator, after consultation with the Sponsor-designated Medical Monitor, determines that a systemic hypersensitivity reaction has occurred related to IMP administration, the participant should be discontinued.

Excluded Therapeutic Agent

If the participant requires treatment with an excluded therapeutic agent and temporary discontinuation cannot be met, IMP should be discontinued.

If a participant discontinues from the trial prematurely, reasonable efforts should be made to perform the Early Termination (ET) visit procedures as soon as possible, and schedule Follow-up Visit procedures 4 weeks after the last dose of ASN51.

7.1.2 Temporary Discontinuation

Drug holidays of up to 4 days (in a 12-week period) are allowed if the participant experiences an AE that necessitates a temporary discontinuation of trial intervention, based on clinical judgment of the Investigator. Consult the Medical Monitor should these events occur.

Any drug holiday (planned or medically indicated) exceeding 7 consecutive days in duration may result in discontinuation from the trial, at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

7.1.3 Rechallenge

Generally, rechallenge will not be allowed.

7.2 Participant Withdrawal from Trial

In accordance with the Declaration of Helsinki, participants have the right to withdraw from the trial at any time for any reason. The Sponsor should be notified of all participant withdrawals as soon as possible.

The primary reason for the participant's withdrawal from the study must be recorded in the participant's eCRF.

Participants must undergo an ET Visit unless withdrawal is due to death or withdrawal of consent.

7.3 Lost to Follow-up

If a participant misses one or more scheduled visits, site personnel will perform the following prior to discontinuation as lost to follow up:

- Contact the participant to reschedule the missed visit and counsel the participant on the importance of safety monitoring
- A minimum of 3 documented attempts to contact the participant (via telephone and written or electronic communication). These contact attempts should be documented in the participant's medical record
- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 Trial Stopping Rules

Should any of following events occur, the SRC, Sponsor, and Coordinating Investigator (along with involved Investigator(s)) will convene on *ad hoc* basis (not to exceed 5 business days after knowledge of the event):

- Death of any participant within 28 days of receipt of IMP unless inextricably related to an alternative cause
- Two or more participants in a group show a 2nd degree AV block, or Mobitz type 2 confirmed with 2 consecutive ECGs, or 3rd degree AV block

- Hy's law is met for one participant, requiring all the following:
  - ALT or AST > 3 × ULN
  - TBL > 2 × ULN
  - ALP < 2 × ULN
  - No other obvious reason for the liver injury, such as viral hepatitis, alcohol use, or another hepatotoxic drug
- AEs occurring in the same System Organ Class (SOC; irrespective of severity or seriousness) leading to discontinuation of trial intervention in 3 or more participants.

All available information regarding the event(s) will be evaluated. Based on reasonable clinical judgment, a decision will be made whether or not the event(s) needs to be further characterized with respect to progression and reversibility; and whether it is reasonable to alter ongoing treatment (criteria/monitoring), recommend a pause in further enrollment, or recommend stopping the trial.

8 TRIAL ASSESSMENTS AND PROCEDURES

The Schedules of Activities for the Screening Period and Treatment/Observation Periods, including allowed visit windows, assessments, and procedures are detailed in:

- Table 1 Schedule of Activities: Screening Period
- Table 2 Schedule of Activities: Double-blind Intervention Period
- Table 3 Schedule of Activities: Long-term Extension Period

Guidelines for study procedures and assessments are discussed briefly in the following sections. Consult the Study Reference Manual for additional information, including a recommended order of (specific) assessments for each visit.

8.1 Screening/Baseline Assessments

Screening for eligibility will be conducted using a tiered approach and may be completed over multiple days (see Section 4.1). The duration of the Screening Period may be up to 8 weeks to allow for the completion of assessments and for the evaluation of required laboratory, ECG, and imaging tests. If additional time is required this will be considered and approved on a case by case basis by the Sponsor Medial Monitor.

A non-contrast brain MRI is performed as the final test for eligibility. If a brain MRI or tau PET scan is not available within the screening window, the Screening Period may be extended, if all other eligibility criteria have been met, by up to 14 days to provide additional time for the imaging results to become available. If the screening window is extended for an individual, repeat clinical chemistry, hematology, and coagulation panels. Results of the repeated laboratory tests are to be reviewed by the Investigator or a qualified designee for final assessment of eligibility.

The Investigator must review and confirm eligibility prior to randomization. Once all eligibility criteria have been met, the Day 1 visit should be completed as soon as possible.

8.1.1 Informed Consent

An abbreviated prescreening informed consent process may be utilized to conduct initial prescreening (i.e., denoted Tier 1 and Tier 2 per Table 1), if allowed at the investigative site. Prescreening consent does not require the study partner.

Informed consent for the full trial must be obtained prior to performing any Tier 3 and Tier 4 screening procedures per Table 1. Informed consent will also be obtained from a designated study partner prior to the Day 1 visit (not required for the abbreviated prescreening consent). The study partner should be an individual who is in contact with the participant for at least 10 hours each week, and agrees to accompany the participant to study visits, or is available by telephone.

8.1.2 Medical History and Demographics

Medical history includes active conditions, and any medical illnesses, diagnoses, and surgeries considered clinically relevant by the Investigator.

The review will also include a detailed assessment of AD, including:

- date of symptom onset and clinical presentation
- date and method of diagnosis
- prior and ongoing treatments, surgeries, or therapies
- prior (or current) participation in interventional clinical trials.

Demographic information (date of birth, sex, race, ethnicity) will be recorded at Screening (as allowed by local regulations).

8.1.3 Phosphorylated tau-217

Participants who meet Tier 1 eligibility criteria, including MMSE, should proceed to Tier 2 (includes plasma pTau217). The time and date of the plasma pTau217 test should be recorded on the Lab Requisition Form. Participants may proceed to Tier 3 screening assessments once evidence of qualifying pTau217 is met.

Plasma phosphorylated tau 217 (pTau217) is a non-invasive diagnostic test shown to accurately predict the likelihood for an individual to have Alzheimer's disease brain amyloid pathology (Ashton, Brum et al. 2024, Therriault, Woo et al. 2024). The incorporation of the plasma pTau217 biomarker in ASN51-201 is intended to identify early AD patients with evidence of brain amyloid pathology, to facilitate trial screening, and to enable the recruitment of diverse participants by avoiding traditional costly and invasive diagnostic AD tests like amyloid beta PET imaging and CSF amyloid testing.

The plasma pTau217 eligibility result is to be reported to the site in the units of pg/mL. If the plasma pTau217 result does not meet criteria for eligibility, the participant is not to complete any additional screening, and will be considered a screen failure.

Further details on the plasma pTau217 assay can be found in the study Laboratory Manual.

8.1.4 Apolipoprotein E Genotyping

Carriers of the apolipoprotein E (APOE) ε4 genotype are at an increased risk for developing sporadic late-onset Alzheimer's disease and cerebral amyloid angiopathy. APOE4 also influences the rate of clinical progression of AD. A blood sample will be obtained for APOE genotyping. APOE status may be disclosed to the Investigator and participant.

8.1.5 Height

A standing height will be measured and recorded using a stadiometer.

8.1.6 Virology Screen

Participants will be screened for hepatitis B surface antigen (HbsAg) and hepatitis C antibody.

8.2 Efficacy Assessments

The assessments and procedures to support trial objectives and derive specified efficacy endpoints (Section 3) are briefly described in the following sections. Timing of assessments is summarized in Section 1.3. Consult the Study Reference Manual for more information.

8.2.1 Cognitive and Functional Assessments

Whenever performed on the same day, cognitive and functional assessments should be performed before procedures that may be stressful for participants (e.g., MRI, PET, blood draw, or CSF sampling).

Raters involved in administering the cognitive function assessments will be blinded throughout the trial. To avoid issues with inter-rater variability, efficacy assessments should be administered by the same individual at the investigative site at approximately the same time of day throughout the duration of participation, where possible.

Data obtained from the ADAS-Cog13, MMSE, and CDR-SB will also be used to derive the ADCOMS.

8.2.1.1 Mini-Mental State Exam (Version 2)

The MMSE is a standardized assessment of mental status and evaluates 7 cognitive domains: orientation to time and place; registration and recall of 3 words; attention and calculation; language; and visual construction (Folstein, Folstein et al. 1975). The instrument is widely used as a brief screen of cognitive abilities (Hall, Forjaz et al. 2015). Administration time is approximately 10 minutes. The MMSE is also administered during pre-screening.

8.2.1.2 Alzheimer's Disease Assessment Scale-Cognitive 13

The modified Alzheimer's Disease Assessment Scale (ADAS-Cog 13) (Mohs, Knopman et al. 1997) includes all original ADAS-Cog items and extends the cognitive domains and range of symptom severity without a substantial increase in the time required for administration. The ADAS-Cog13 consists of 13 items that are commonly impaired in Alzheimer's Disease: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures. Scores range from 0 to 85; higher scores indicate greater severity. Administration time is approximately 30 minutes.

8.2.1.3 Clinical Dementia Rating – Sum of Boxes

The Clinical Dementia Rating – Sum of Boxes (CDR-SB) is a 5-point scale to characterize 6 domains of cognitive and functional impairment simultaneously (Coley, Andrieu et al. 2011). The CDR is obtained through semi structured interviews of participants and study partners. The

score is used to characterize and track the level of impairment/dementia. The CDR-SB can be used to accurately stage AD and discriminate between very early AD and those with mild cognitive impairment (O'Bryant, Waring et al. 2008).

8.2.2 Imaging Assessments

Acquiring MRI images in conjunction with ^{18}F MK-6240 PET is permitted if dual PET/MRI imaging devices are utilized.

8.2.2.1 ^{18}F MK-6240 PET Scan

Positron emission tomography (PET) imaging of NFT tangle pathology with the tau tracer MK-6240 is a biomarker method to measure the effect of ASN51 on the progression of AD tau NFT pathology.

[redacted]

Additional information is available in the Imaging Manual.

8.2.2.2 Volumetric Magnetic Resonance Imaging

An MRI will be performed as part of Screening. The MRI scan will be submitted to the central MRI vendor for final determination of eligibility. Results of centrally read MRIs will be used for data analysis and reports; relevant safety and eligibility results will be communicated back to the site. Volumetric MRI will be performed to assess changes in whole brain, ventricular and select region of interest and cortical thickness volumes.

Additional information is available in the Imaging Manual.

8.3 Safety Assessments

Assessments to characterize safety and tolerability of ASN51 are described below; associated safety endpoints and planned analyses are described in Section 3 and Sections 9.2 and 9.6, respectively.

8.3.1 Physical Examination

Complete physical examinations will be performed by the Investigator or designated licensed professional (MD, NP, RN, PA, or equivalent).

A complete physical examination includes general appearance; head, eyes, ears, nose, and throat; and cardiovascular, dermatologic, respiratory, gastrointestinal, musculoskeletal, and neurologic systems (include neurological assessment of cranial nerves, motor, sensation, coordination, reflexes, and gait).

Findings will be recorded as normal/abnormal for each parameter with additional description as indicated.

8.3.1.1 Weight

Weight (measured in kilograms) and height (in meters) will be measured and recorded during each physical examination. Participants may remain in clothes.

8.3.2 Vital Signs

Vital signs include seated systolic and diastolic blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (°C). Measurements should be obtained after the participant has been seated for a minimum of 5 minutes, and before any additional assessments are completed.

8.3.3 Electrocardiogram

A routine 12-lead ECG will be performed after the participant has rested for a minimum of 5 minutes in the supine position. All ECGs must be performed and recorded in triplicate. Triplicate ECGs should be taken at approximately 1-minute intervals. Obtain ECGs, to the best of the site and participants' ability, at approximately the same time of day at each visit to minimize diurnal variation.

8.3.3.1 ECG Parameters

ECG Parameters include PR interval, QRS duration, QT interval, and QTcF. ECG administration procedures will be standardized, and results will be read centrally by qualified personnel blinded to treatment assignment, timepoint, and participant data.

ECGs will be transmitted to and interpreted by a central vendor as normal or abnormal, with clinical significance determined by the Investigator.

8.3.4 Clinical Laboratory Assessments

Laboratory assessments will be used routinely to assess eligibility and IMP safety in all participants per Table 1 and Table 2, respectively. After initiation of IMP, clinically significant abnormal laboratory findings must be documented as an AE. Clinical laboratory parameters to be assessed for safety are listed in Section 13.2. The Study Reference Manual provides details on sample collection and processing.

Fasting is not required; fasting status will be recorded.

All laboratory assessments will be conducted by a central laboratory unless otherwise specified.

8.3.4.1 Serum Chemistry

Blood samples will be obtained for serum chemistry parameters (comprehensive metabolic panel) as noted in Section 13.2.

8.3.4.2 Hematology

Blood sample will be obtained for hematology parameters (complete blood count with differential) as noted in Section 13.2.

8.3.4.3 Urinalysis

A urinalysis panel (dipstick with microscopic examination on positives) will be performed with parameters as noted in Section 13.2.

8.3.4.4 Coagulation Panel

A coagulation panel will be performed with parameters as noted in Section 13.2.

8.3.4.5 Serum Hormone Markers

Serum hormone markers will be obtained as outlined in Section 13.2.

8.3.5 Suicidal Ideation and Behavior Risk Monitoring

8.3.5.1 Columbia Suicide Severity Rating Scale

To prospectively assess suicidal ideation and behavior, the C-SSRS will be administered by site personnel. The "Screen Version" questionnaire will be administered at Screening. The "Since Last Visit" questionnaire will be administered at all subsequent visits. Depending on the cognitive state of the participant, some questions within the C-SSRS may be deemed inappropriate by the Investigator and/or site personnel and may be omitted.

Integration of information from other sources (e.g., family, friends, or significant others; study partners or health professionals; hospital or emergency room records) may be evaluated and integrated into the assessment as appropriate.

Responses will be reviewed during the visit; if emergent suicidal ideation or behavior is indicated, the Investigator will promptly evaluate the participant to ensure proper management and participant safety.

8.4 Adverse Events and Serious Adverse Events

Definitions, recording, follow-up, and reporting requirements for AEs and SAEs follow routine pharmacovigilance practice are provided in Section 12.

Trial-specific guidance is provided in the following subsections.

8.4.1 Time Period and Frequency for Collecting Adverse Event Information

All AEs, SAEs, AESI, and partner pregnancies occurring during the protocol-specified timeframes (Table 7) will be assessed and reported per guidelines provided in Section 12.

Table 7 Adverse Event Reporting Periods

Event Type	Reporting Period	Additional Requirements
AE/SAE during Screening Period	Date of participant informed consent through start of Day 1 Visit (prior to first dose of IMP)	Report as AE/SAE only if related to trial-specified procedure (medical history otherwise)
Treatment-emergent AE/SAE	First dose of IMP through 4 weeks post final dose of IMP	Report SAEs outside of reporting period if assessed as related to IMP
AESI	First dose of IMP through 4 weeks post final dose of IMP	Report AESI outside of reporting period if assessed as related to IMP
Pregnancy of partner	Date of participant informed consent through 4 weeks post final dose of IMP	Obtain consent to follow partner pregnancy

AE = adverse event; AESI = adverse event of special interest; IMP = investigational medicinal product; SAE = serious adverse event.

Clinically significant changes from baseline in any safety or clinical laboratory parameter will be recorded as AEs or SAEs, if deemed appropriate by the Investigator.

8.4.2 Identifying Adverse Events and Serious Adverse Events

At each visit, participants will be asked about any new or ongoing AEs since the previous visit. Spontaneous reporting of AEs and SAEs will be encouraged.

8.4.3 Adverse Events of Special Interest

Events defined below are considered AESI for this trial and should be reported following SAE reporting procedures (Section 12.3).

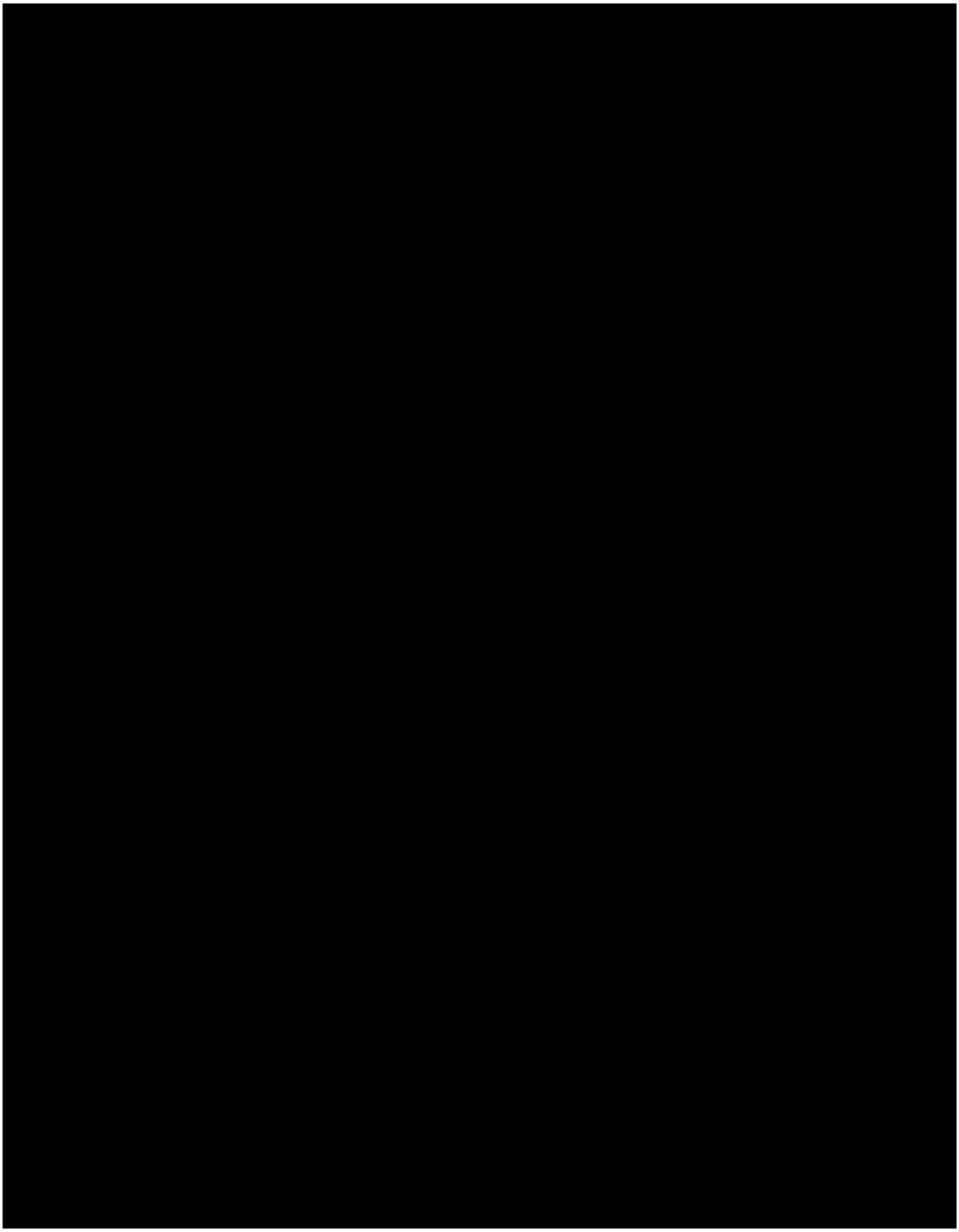
8.4.3.1 Drug Induced PR Prolongation

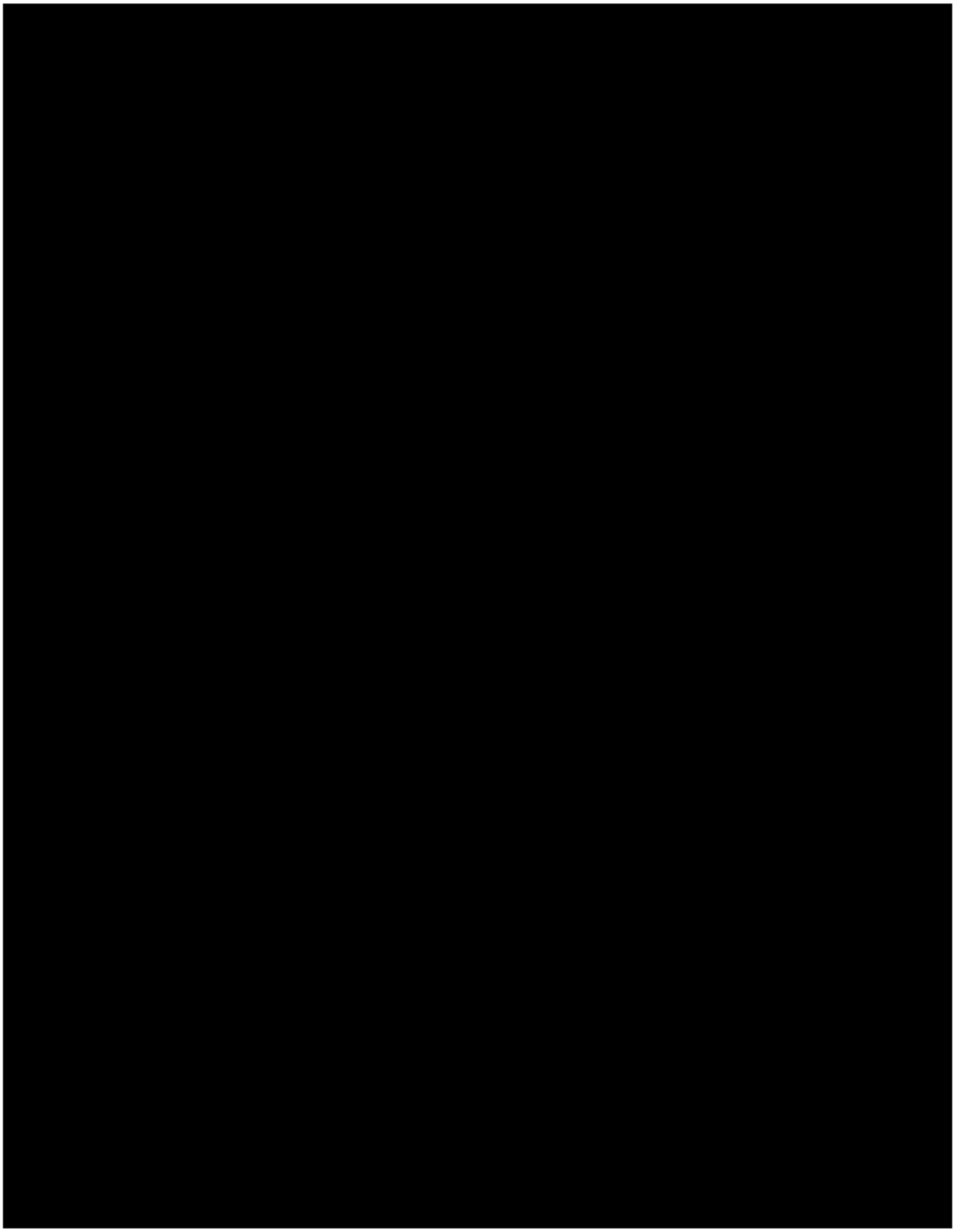
Drug-induced PR prolongation with Mobitz type 1 second degree AV block may be a risk associated with ASN51. TEAEs with the following Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) will be considered an AESI for this trial:

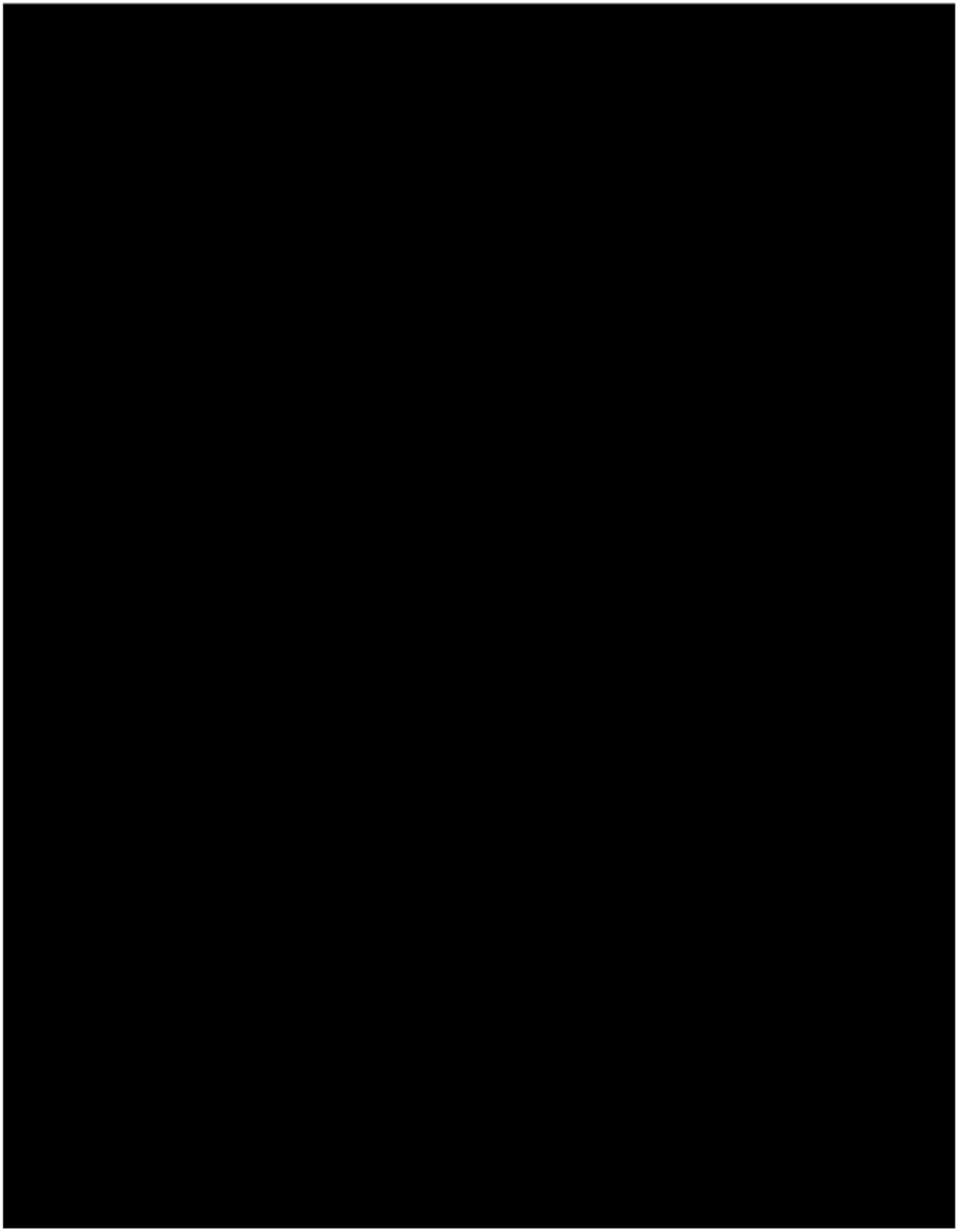
- AV block first degree, AV block second degree Mobitz type I, AV block second degree Mobitz type II, and AV block third degree.

8.4.3.2 Drug Induced Liver Injury

The potential for drug-induced liver injury will be monitored using assessments of liver function via serum chemistry at regular intervals. If the AST or ALT is $> 1 \times$ ULN but $< 2 \times$ ULN, the Investigator should determine whether more frequent testing is warranted. If the AST or ALT is $\geq 2 \times$ ULN with or without bilirubin or alkaline phosphatase elevation, but do not meet the







8.10 Immunogenicity

Not applicable.

8.11 Medical Resource Utilization and Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

A general description of the statistical methods planned to analyze the safety and preliminary efficacy of the IMP is outlined below. The analyses specified in this protocol will be expanded in the Statistical Analysis Plan (SAP) to include a detailed description of the analyses. The SAP will be finalized and approved prior to database lock.

Trial data will be reported using summary tables, figures, and data listings. Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, median, minimum, and maximum will be provided. For discrete data, incidence and percentages will be provided. Statistical tests will be 1-sided at the alpha level of 0.10, unless stated otherwise. P-values will be used descriptively and will have no inferential value. All p-values will be reported to the 3rd decimal place. Summary tables will include the data from the ASN51 [redacted] groups combined, i.e., Placebo and ASN51 [redacted] for the DB and LTE periods, respectively.

Baseline for all clinical laboratory evaluations, vital signs measurements, and 12-lead ECGs will be defined as the last evaluation before IMP administration. The timing of each protocol-specified assessment is provided in the Schedules of Activities (Section 1.3).

Two sets of analyses will be conducted. The first set of analyses will be conducted after all participants have had the opportunity to complete the Week 24 assessment or have discontinued the study (primary analysis Sections 9.1 through 9.7). The second set of analyses will be conducted when all participants have had the opportunity to complete the LTE or discontinued the study (Section 9.8).

For endpoints collected only once post-baseline, changes from baseline will be analyzed using an analysis of covariance (ANCOVA) model that includes the categorical effects of APOE4 status, use of AD medication, treatment group, and the continuous covariate of the baseline value of the variable being analyzed. The one-sided p-value (t-test on least squares means at Week 24) and two-sided 80%, and 90% confidence limits will be tabulated. The model will also include the randomization stratification factors (i.e., APOE4 status and use of AD medication).

For endpoints collected multiple times post-baseline, changes from baseline will be analyzed using a restricted likelihood-based mixed effects model for repeated measures (MMRM). Change from baseline will be fit as the dependent variable. Independent variables included in the analysis model will be the categorical fixed effects of APOE4 status, use of AD medication, treatment group, and the treatment by Visit interaction, along with the continuous covariates of the baseline value of the variable being analyzed and its interaction with Visit. The model will also include the randomization stratification factors (i.e., APOE4 status and use of AD medication). Within participant errors will be modeled using an unstructured covariance matrix. If this analysis fails to converse, heterogeneous Toeplitz, heterogeneous auto-regressive, and heterogeneous compound symmetric structures will be tested in the listed order. The first structure to yield

convergence will be considered the primary analysis. The one-sided p-value (t-test on least squares means at Week 24) and two-sided 80%, and 90% confidence limits will be tabulated.

Analysis of PK parameters may be described and summarized in a separate document outside the context of the SAP.

Data analysis will comply with principles set forth in the International Conference on Harmonisation (ICH) E9 Guideline and ICH E9(R1) Guideline.

9.1 Analysis Sets

The number of participants randomized who complete each trial Period and who discontinue the trial will be summarized. Reasons for discontinuation will be summarized. The following analysis sets will be employed:

9.1.1 Modified Intent-to-Treat

The modified Intent-to-Treat (mITT) Analysis Set will include all participants who received at least one dose of IMP. Participants will be included in the assigned dose cohort/arm, regardless of the actual treatment received.

9.1.2 Safety Analysis Set

The Safety Analysis Set consists of all participants who receive at least one dose of IMP. This analysis set will be used for the analyses of all safety endpoints. Participants will be included based on the actual dose level received.

9.1.3 Per Protocol Set

The Per Protocol Analysis Set will consist of participants who did not have major protocol violations with regard to entry criteria, adherence to IMP dosing, disallowed concomitant medications, and completion of study visits and procedures. A detailed list of participants with major protocol violations will be determined and documented prior to unblinding.

9.1.4 Pharmacokinetic Analysis Set

The PK Analysis Set will consist of all participants from whom plasma or CSF samples for the analysis of ASN51 were obtained and who did not have major protocol deviations that would confound interpretation of PK analysis.

9.2 Analysis Supporting Primary Objective - Safety

All safety analyses will be conducted in the Safety Analysis Set.

Adverse Events

Safety will be evaluated by examining incidence, type, causality, and severity of TEAEs, including SAEs and discontinuation due to TEAE.

Adverse events will be classified according to the latest available MedDRA version, to the SOC and PT levels. Treatment-emergent AEs (hereafter referred to as AEs) are defined as those with onset after the first dose of randomized treatment intervention at Day 1 or, if occurring prior to administration of the first dose at Day 1, worsened after administration of that first dose.

The AE listings will indicate whether the event led to temporary interruption of or permanent withdrawal of study treatment. An overall summary will be presented which gives the number and percentage of participants within each dose group in the safety population that experienced any AE, experienced any treatment-related AE, temporarily interrupted or permanently discontinued treatment due to an AE, experienced an SAE, and that died.

Incidence of Adverse Events

The number and percentage of participants experiencing one or more AE within a MedDRA SOC and PT without regard to intensity, relationship, or seriousness will be tabulated.

Tables will also be prepared to display events by SOC, PT, and maximum intensity or closest relationship to treatment.

A glossary listing that shows the verbatim terms assigned to each SOC and PT will be provided.

Severity of Adverse Events

A summary of AEs by severity will be presented in a table by incidence of occurrence. The severity that will be presented represents the most extreme severity captured on the eCRF page. The severity will be assessed by the Investigator as "Mild," "Moderate," or "Severe." If a participant reports multiple occurrences of the same AE (at the PT within the SOC level and at the SOC level), only the most severe will be presented.

Relationship of Adverse Events to Study Treatment

A summary of AEs by relationship to study treatment will be presented in a table by incidence of occurrence. The relationships will be collected based on the Investigator's determination of likelihood that study treatment could have caused the event. The possible relationships are "Unrelated", "Unlikely", "Possibly," "Probably," and "Definitely." For the summary of relationships, the categories of "Possibly," "Probably," and "Definitely" will be combined to form a single category of "Related." In the AE relationship table, if a participant reports multiple occurrences of the same AE (at the PT within SOC level and at the SOC level), only the occurrence with the greatest causal relationship will be presented. AEs that are missing relationship data will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship.

Adverse Events Leading to Treatment Discontinuation

All AEs for which the action "Study treatment discontinued" is recorded will be tabulated.

Serious Adverse Events

The data for SAEs will be presented in a listing. If a sufficient number of SAEs are reported, the severity and relationship tables can be subsetted on the SAE subpopulation.

Death

The data for participant deaths, if any, will be presented in a listing.

Changes from baseline in clinical laboratory test values, physical and neurologic examination results, vital signs measurements, and 12-lead ECGs will be listed and/or summarized through the end of trial.

9.2.1 Adverse Events

The original terms used in the eCRFs by investigators to identify AEs will be coded using the latest available MedDRA version. The number and percentage of participants with TEAEs will be summarized by treatment group. Summaries will be developed for those participants who discontinued treatment due to an AE or who experienced a life-threatening or treatment-emergent SAE.

9.2.2 Statistical Model, Hypothesis and Method of Analysis

Given the exploratory nature of the study, no formal statistical hypothesis will be performed. Nominal p-values for safety endpoints will be reported for descriptive purposes. Analyses will be based on Fisher's Exact Test.

9.2.3 Handling of Missing Data

Adverse events with missing or partial onset date will be treated as TEAEs unless the partial onset date or end date of the event is complete enough to indicate that the event started or resolved prior to the first administration of the study intervention, in which case it will be documented in medical history. If AE grade or relationship is missing in analyses of grade and causality, the missing grade will be set to severe, and relationship will be set to related for tabulation purposes. Procedures for imputation of missing or partial AE start and end dates will be specified in the SAP.

Handling of missing data for secondary efficacy endpoints is described in Section 9.3.

9.3 Analysis Supporting Key Secondary Objectives

The following family of endpoints that each assess tau pathophysiology will be used to determine proof-of-concept. These endpoints will be tested together to control the family-wise error rate at the desired alpha of 0.10.

- Change in CSF pTau217 [Time frame: baseline to Week 24]
- Change in plasma pTau217 [Time frame: baseline to Week 24]
- Change in CSF total tau [Time frame: baseline to Week 24]

The estimand for these endpoints is specified as follows:

Treatment regimens:	• ASN51 [redacted], ASN51 [redacted], or placebo, once daily
Population:	• Early Alzheimer's Disease, as described by study inclusion / exclusion criteria (Sections 5.3 and 5.4) • The mITT population will be used in the analysis
Endpoints	• CSF pTau217, plasma pTau217, CSF total Tau
Summary statistic	• Difference between treatments in mean change from baseline to Week 24
Intercurrent events	• A treatment policy strategy will be used to account for deviations in study medications and in use of concomitant medications. • Data as collected will be analyzed without multiple imputation via ANCOVA or MMRM as appropriate. • As sensitivity analyses, missing data will be multiply imputed under the missing not at random assumption using both jump to placebo (reference) based imputation and the tipping point methodologies.

ANCOVA = analysis of covariance; CSF = cerebrospinal fluid; mITT = modified Intent-to-Treat; MMRM = mixed effects model for repeated measures.

Descriptive statistics for each endpoint will be summarized for each visit where that endpoint is assessed. The ANCOVA analysis described in Section 9 will be used to assess CSF pTau217 and CSF total Tau as the endpoints are collected only once post-baseline. The MMRM analysis described in Section 9 will be used to assess plasma pTau217, which is collected repeatedly post baseline. For sensitivity analyses of the key secondary endpoints, missing data will be imputed using the multiple imputation technique under the missing not at random assumption using both placebo (reference) based imputation and the tipping point method.

Multiplicity across these 3 endpoints and 2 dose arms will be controlled in the following manner. Testing will begin with the [redacted] dose using the Hochberg step up procedure. The results for these 3 endpoints will be ordered from smallest to largest p value within the [redacted] arm. Significance will be based on testing the largest p value at $\alpha = 0.1$, the 2nd endpoint in the order will be tested at $\alpha /2 = 0.05$, and the 3rd endpoint will be tested at $\alpha / 3 = 0.033$. If any of the 3 tests within the [redacted] arm are significant, the secondary endpoint is considered met for the [redacted] dose and testing will proceed to the [redacted] arm using the 0.1 significance level.

9.4 Analysis Supporting Other Secondary Objectives

9.4.1 18F MK-6240 PET Scan

Tau burden, assessed using ^{18}F-MK-6240 standardized uptake value ratio (SUVR), will be calculated in a volume weighted composite medial temporal region of interest (ROI), encompassing the entorhinal cortex, amygdala, parahippocampal cortex, and hippocampus (Jack, Wiste et al. 2017, Sanabria Bohorquez, Baker et al. 2024). The following family of endpoints that each assess tau pathophysiology will be used to determine proof-of-concept.

The following endpoint will be tested at the desired one-sided alpha of 0.10.

- Change in SUVR in the medial temporal ROI [Time frame: baseline to Week 24]

The estimand for this endpoint is specified as follows:

Treatment regimens:	• ASN51 [redacted], ASN51 [redacted], or placebo, once daily
Population:	• Early Alzheimer's Disease, as described by study inclusion / exclusion criteria (Sections 5.3 and 5.4) • The mITT population will be used in the analysis
Endpoints	• Tau PET medial temporal ROI SUVR
Summary statistic	• Difference between treatments in mean change from baseline to Week 24
Intercurrent events	• A treatment policy strategy will be used to account for deviations in study medications and in use of concomitant medications. • Data as collected will be analyzed without multiple imputation via ANCOVA or MMRM as appropriate. • As sensitivity analyses, missing data will be multiply imputed under the missing not at random assumption using both jump to placebo (reference) based imputation and the tipping point methodologies.

ANCOVA = analysis of covariance; CSF = cerebrospinal fluid; mITT = modified Intent-to-Treat; PET = positron emission tomography; ROI = region of interest; SUVR = standardized uptake value ratio.

Descriptive statistics will be summarized for each visit where that endpoint is assessed. The ANCOVA analysis described in Section 9 will be used to assess tau PET medial temporal ROI SUVR as the endpoint is collected only once post-baseline in the DB intervention period.

9.4.2 ASN51 Pharmacokinetics

Pharmacokinetic analysis will be performed on the PK Analysis Set.

Plasma concentrations of ASN51 will be analyzed using noncompartmental methods to determine the relevant PK parameters. The ASN51 concentrations and PK parameters will be listed and summarized by study day (and timepoint, as appropriate) and dose group. Individual and mean concentration profiles over time will be provided by participant/dose group and study day.

Details on the PK analyses will be in the SAP that will be finalized before database lock. Any integrated analyses across studies, such as a population PK analysis will be presented separately from the main CSR.

9.5 Analysis of Exploratory Objectives

Analyses of exploratory biomarkers and efficacy endpoints will include difference between treatments in mean change from baseline to Week for additional CSF biomarkers (including but not limited to [redacted]

Absolute values and changes from baseline will be summarized using descriptive statistics by visit (and timepoint) and by dose group. Supportive plots will be generated as appropriate.

Details will be specified in the SAP which will be finalized before database lock for the DB Intervention period.

9.6 Additional Safety Analysis

Described in Section 9.2 and further delineated in subsections below.

9.6.1 Physical Examination

Baseline physical examination will be summarized in a frequency table by body system to characterize the enrolled Safety Analysis Set. Shift tables will be presented for each body system showing the change from baseline in status between Normal/Abnormal at each assessment.

9.6.2 Body Weight

Baseline body weight will be summarized using the descriptive statistics outlined in Section 9 to characterize the enrolled Safety Population. Changes from baseline will be described using the descriptive statistics for continuous outcomes. In addition, potentially clinically meaningful changes will be evaluated using the descriptive statistics for categorical endpoints described. The definitions of clinically meaningful changes will be provided in the SAP.

9.6.3 Vital Signs

Vital signs include blood pressure, heart rate, respiration rate and body temperature. Vital signs data will be listed and summarized using descriptive statistics for absolute values, and changes from baseline by visit and dose group. In addition, potentially clinically meaningful changes will be evaluated using the descriptive statistics for categorical endpoints. The definitions of clinically meaningful changes will be provided in the SAP.

9.6.4 Electrocardiogram Parameters

ECG parameters of interest include PR interval, QRS duration, QT interval, and QTcF. Baseline values will be summarized by descriptive statistics to characterize the Safety Population. Changes from baseline will be summarized using the descriptive statistics described in Section 9 for continuous outcomes. In addition, potentially clinically meaningful changes will be evaluated using the descriptive statistics for categorical endpoints. The definitions of clinically meaningful changes will be provided in the SAP.

9.6.5 Clinical Laboratory Panels

Clinical laboratory panels include serum chemistry, hematology, and urinalysis, as well as coagulation and serum hormone markers. Baseline values will be summarized by descriptive statistics or frequency tables, where appropriate, to characterize the Safety Analysis Set. Changes from baseline will be summarized using the descriptive statistics described in Section 9 for continuous outcomes. In addition, the count and percentage of participants with at least one clinically significant abnormal value by visit and post treatment will be summarized by dose group. Data listings of abnormalities will also be provided as appropriate.

9.6.6 Columbia Suicide Severity Rating Scale

Baseline and post-baseline results for the C-SSRS will provided in patient listings. The count and percentage of participants with suicidal behavior and suicidal ideation (as assessed by C-SSRS) will be summarized by visit and dose group.

9.7 Other Analysis

Demographics (age, gender, race, ethnicity, and region) and other baseline disease characteristics, including APOE4 genotype, will be summarized using descriptive statistics.

Analyses of biomarkers, pharmacogenomic, and PK data will be described in separate reports outside the context of the SAP.

9.8 Analyses for Long-term Extension

For the LTE, the incidence and severity of AEs over the placebo-controlled and long-term extension periods of the study will be summarized from LTE baseline to the end of treatment by DB Intervention Period treatment assignment and overall. Other safety parameters will be summarized as described for the DB Intervention Period primary analysis in Section 9.6.

Analyses for the LTE will use the same methods as described for the DB Intervention Period analysis in Sections 9.3 through 9.5. Summaries will be provided for changes from LTE baseline by DB treatment assignment and overall. For participants switching from placebo to active treatment, a two-slope random coefficient model will be used to compare the change in biomarkers and efficacy assessments from DB baseline to Week 24 (e.g., end of DB Intervention period) and from the LTE baseline (e.g., Week 24) to Week 60 (end of LTE).

A full description of LTE analyses will be provided in the SAP.

9.9 Timing of Analysis

Reviews of safety, PK, and clinical efficacy data will be performed as specified in Section 4.1.

The primary analysis will be conducted following completion of the DB Intervention Period.

The final analysis will be conducted at the end of the LTE; results will be presented in a final clinical study report.

9.10 Sample Size Determination

The sample size was not derived statistically, but empirically determined based on the safety objectives of this dose ranging trial. With N = 21 per arm (accounting for a 20% dropout rate), the rule of 3 suggests that the probability of observing at least 1 occurrence of individual AEs is at least 95% if the incidence rate is greater than 1/(N/3), which is approximately 14%.

For the plasma and CSF key secondary biomarker endpoints (CSF pTau217, plasma pTau217, and CSF tTau), the study has 90% power at a one-sided alpha of 0.1 to observe a baseline-adjusted change from baseline of 20% relative to placebo assuming a 25% standard deviation (e.g., Cohen's d of 0.8). A difference of 20% from placebo has been observed for CSF tTau and pTau with the OGA inhibitor Thiamet G in the rTg4510 tau model (Wang, Smith et al. 2018) and is a similar effect size to what has documented after 24-weeks of treatment of early AD patients with amyloid lowering therapies like lecanemab and donanemab (Salloway 2023, van Dyck, Swanson et al. 2023).

9.11 Protocol Deviations

Any deviations in the study protocol will be documented and reported in accordance with IRB requirements. No deviation from the protocol will be implemented without the prior review and approval of the IRB/IEC except where it may be necessary to eliminate an immediate hazard to a

research participant. In such case, the deviation will be reported to the IRB/IEC as soon as possible.

10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

The trial will be conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki, applicable ICH Good Clinical Practice (GCP) Guidelines, and applicable local laws and regulations. Should a conflict arise, the Investigator will follow whichever law or guideline affords the greater protection to the individual participant.

The protocol, protocol amendments, Informed Consent Form (ICF), IB, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Protocol amendments require IRB/IEC approval before implementation of changes to the trial design, except for changes necessary to mitigate an immediate hazard to participants.

10.2 Committees

10.2.1 Ethics Committees

The IRB/IEC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." The protocol, any protocol amendments, and the associated ICFs must be reviewed and approved by the IRB/IEC prior to screening of any potential participant. IMP may not be shipped to the Investigator until Sponsor, or its designee has received a copy of the letter or certificate of approval from the IRB/IEC for the protocol and any protocol amendments, as applicable.

All participant recruitment and/or advertising information must be submitted to the IRB/IEC and Sponsor or its designee for review and approval prior to implementation. IRB/IEC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect participant safety. In such cases, the chair of the IRB/IEC should be notified immediately, and the amendment forwarded to the IRB/IEC for review and approval.

10.2.2 Safety Review Committee

The SRC will be formed to review safety and tolerability data and will meet on an ad hoc basis if requested by one of the members or if trial stopping rules are met as outlined in Section 7.4. The SRC will be comprised of the Sponsor's Medical Monitor, a pharmacovigilance monitor, and the trial Investigator. The SRC may, based on the nature, frequency, and/or severity of an adverse event recommend protocol modification(s), dose suspension, dose termination or study

termination. A Safety Review Committee charter will provide full guidance on the function and practices to be followed by the SRC.

10.3 Informed Consent Process

Appropriate forms for documenting written informed consent will be reviewed and approved by the Sponsor or its designee prior to investigator submission to the IRB/IEC. The Sponsor or its designee must receive a copy of the IRB/IEC's approval of the ICF before the shipment of IMP to the trial site.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements.

The Investigator is responsible for obtaining written informed consent from each potential trial participant and study partner prior to the conduct of any trial procedures. The signed ICF must be retained in each participant's trial file and be accessible to the trial monitor. Participants will be given a copy of the signed ICF and will be provided with any new information during the course of the trial that might affect their continued participation in the trial.

If the protocol is amended and the ICF is revised, each participant will be required to provide written informed consent again using the revised ICF.

10.4 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or biological samples that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant will 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 ICF.

The participant will 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.

10.5 Early Site Closure or Trial Termination

The Investigator will have the following responsibilities:

- Providing oversight of trial conduct at the site
- Adhering to 21 CFR, ICH guidelines, IRB/IEC requirements, European Clinical Trials Directive (if applicable), and all other applicable local regulations

- Promptly notifying the IBR/EC of significant safety findings
- Providing trial status updates to the IBR/EC as required
- Provide the Sponsor with required information to complete financial certification or disclosure statement as required by regulatory authorities.

Should the Investigator not comply with these responsibilities, the site may be closed.

The Sponsor or designee reserves the right to close a site or terminate the trial at any time. Likewise, an Investigator has the right to initiate site closure. Reasons for early site closure of a study site by Sponsor or Investigator include but are not limited to:

- Failure to follow Investigator responsibilities, as listed above
- Inadequate recruitment by the Investigator
- Discontinuation of IMP development.

Following termination or suspension, the Sponsor and Investigator will ensure the appropriate ethics committee(s) and regulatory authorities are informed, and participants are notified and transitioned, as appropriate.

11 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

Quality tolerance limits will be predefined by the Sponsor and/or its designee in a study management plan. The plan will include a description of monitoring approaches and the process for handling non-compliance with the protocol or ICH GCP guidelines.

11.2 Data Quality Assurance

Monitoring and auditing procedures developed by Sponsor and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. The following principles will be set forth to ensure quality of trial data:

- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations)
- The Sponsor or designee is responsible for the management of trial data including quality control
- The Sponsor (or designee) will develop a monitoring plan to detail methods, responsibilities, and requirements (including handling of noncompliance issues)
- All participant data relating to the trial will be recorded on the eCRF unless electronically transmitted directly to the Sponsor or designee (e.g., laboratory data)
- Any changes to the data will be made only by Sponsor-authorized users; changes will be captured in an electronic audit trail
- The Investigator is responsible for verifying the accuracy of data entered at the trial site
- Monitors will evaluate the site to assure the safety and rights of participants are being protected; and the trial is being conducted in accordance with the current protocol, trial agreements, ICH GCP, and all applicable regulatory requirements.

11.3 Source Data

- The Investigator will maintain accurate documentation (source data) that supports information entered in the eCRF
- The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents
- Monitors will verify source data to confirm data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable

- Records and documents pertaining to the conduct of this trial (including original signed ICFs), must be retained by the Investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period
- No records may be destroyed during the retention period without the written approval of the Sponsor.
- Written notification to the Sponsor is required prior to any transfer of records to another location or party.

11.4 Contingency Plans During Public Health Emergencies, Natural Disasters, or Other National Emergencies

If an investigational site is affected by a public health emergency, natural disaster, or other national emergency during the trial, the Sponsor will coordinate with the Investigator/Institution to ensure the safety of trial participants in accordance with GCP and available regulatory guidance documents.

The Sponsor will seek to maintain the integrity of the trial, however minimization of risk to trial participants will be considered paramount.

In such unprecedented situations, contingencies may include:

- Suspension of trial recruitment
- Alternate provisions for providing investigational product and supply chain management
- Modifications to monitoring processes and procedures.

The Sponsor will consult with Investigators and IRB/IECs in a timely manner to determine actions needed to protect active trial participants. However, changes to protect the safety of trial participants may be implemented without prior IRB/IEC approval, such as:

- Delayed administration of IMP (i.e., extended screening periods) until safety follow-up may be conducted
- Alternate methods for safety assessments (e.g., telephone, telemedicine, remote location for laboratory sample acquisition and/or processing)
- Postponement of certain visits and/or assessments deemed less critical
- Exceptions to protocol-specified visit windows.

12 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS SEVERITY AND CAUSALITY

12.1 Definitions

12.1.1 Adverse Event Associated with Study Procedures

A procedure-related AE is an AE considered by the Investigator to be related to a procedure required by the protocol (i.e., temporally associated or known risk of the procedure).

12.1.2 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. The term "adverse event" could include any of the following events that develop or increase in severity during the course of the trial. Examples include:

- Any sign, symptom, or physical examination finding that worsens in nature, severity, or frequency compared to baseline irrespective of association with the condition under study
- Any clinically significant laboratory abnormality or laboratory abnormality that requires medication or hospitalization
- Reactions to IMP including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity
- Concurrent illness
- Injury or accident.

Conditions present prior to enrollment are considered Medical History. Pre-existing conditions should be reported as a TEAE if there is a change in the frequency, intensity, or the character of the condition.

12.1.3 Serious Adverse Event

An SAE is an AE that:

- results in death
- is considered life threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent/significant disability/incapacity
- results in a congenital anomaly/birth defect; or
- other medially important serious medical event.

12.2 Recording of Adverse Events and Serious Adverse Events

12.2.1 Severity

The intensity of each AE should be graded as mild, moderate, severe, or potentially life-threatening, using the following categories:

- Mild : asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention generally not indicated
- Moderate : minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Severe : interrupts normal daily activities and generally requires systemic drug therapy or other treatment; usually incapacitating. May also be considered potentially life-threatening or require urgent intervention to prevent permanent impairment, persistent disability, or death

Severity is not considered a guide for defining regulatory reporting obligations.

12.2.2 Causality

The Investigator should consult the IB when assessing relationship to IMP and consider all possible etiologies for the AE. The Investigator will assess the causality of the AE to study procedure or IMP as follows:

Attributions for "Unrelated" events:

- ***Unrelated:*** the AE ***is clearly not related*** to the IMP/procedure, beyond a reasonable doubt
- Unlikely Related: the AE is doubtfully related to the IMP/procedure

Attributions for "Related" events:

- Possibly Related: the AE may be related to the IMP/procedure
- Probably Related: the AE is likely related to the IMP/procedure
- Definitely Related: the AE is clearly related to the IMP/procedure

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Unrelated or Unlikely Related will be considered Unrelated.

AEs listed as related are considered to have a suspected "reasonable causal relationship" to the IMP/intervention (ICH E2A). The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

12.2.3 Follow Up

All AEs (i.e., any new or worsening in severity or frequency of a preexisting condition) with onset after the participant signs consent for trial participation must be promptly documented on the AE eCRF via the electronic data capture system. Details of the AE must include severity, relationship to IMP, duration, and outcome.

Participants who discontinue due to treatment-emergent SAE will be monitored for safety as specified in Section 8.4.1.

Follow-up is required for all participants with AEs until the event has been resolved or the condition has stabilized. Clinically significant abnormal laboratory values should be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

12.2.4 Outcome

The outcome of an AE associated will be assessed as follows:

- Recovered/Resolved: the event has improved or recuperated
- Not recovered/Not Resolved: the event has not improved or recuperated
- Recovered/resolved with sequelae: the participant recuperated but retained pathological conditions resulting from the prior disease or injury
- Fatal: termination of life as a result of an AE
- Unknown: not known, not observed, not recorded

12.3 Reporting of Serious Adverse Events

SAEs and AESIs must be reported to the Sponsor (or designee) within 24 hours of the knowledge of the occurrence.

An SAE report will be completed as thoroughly as possible including all available details about the event and the signature of the Investigator. The SAE form will be updated when additional information is received.

A death occurring during the trial must be reported to Sponsor or its designee within 24 hours of knowledge of the death whether or not it is considered treatment related.

The Investigator also must notify the IRB/IEC of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with IRB/IEC requirements and local law. A copy of this notification must be provided to the Sponsor or its designee.

12.4 Regulatory Reporting Requirements for Serious Adverse Events

Investigators are required to report any urgent safety matters to Sponsor or its designee within 24 hours. The Investigator will notify the IRBs/IECs of SAEs and urgent safety matters, in

accordance with IRB/IEC requirements and local laws and regulations. A copy of this notification must be provided to the Sponsor or its designee.

SAEs that are unexpected and considered related to the administration of the IMP will be reported by the Sponsor (or designee) to the appropriate regulatory authorities and other investigators in the form of an expedited safety report within 15 calendar days after receiving information on the SAE. The investigators will notify their reviewing IRB/IEC and other committee(s) as required by institutional policies.

12.5 Serious and Unexpected Adverse Reaction Reporting

Fatal and life-threatening suspected unexpected serious adverse reactions (SUSARs) will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional eight (8) days. The Sponsor will report any unexpected life threatening or fatal SAEs that are considered related to the IMP to the appropriate regulatory authorities within 7 days of receiving the information.

13 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1 Contraception and Pregnancy Testing

13.1.1 Definitions Related to Childbearing Potential

Females of Childbearing Potential:

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Note: WOCBP are excluded from participation in this trial.

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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Fertile Males:

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

13.1.2 Contraception

Use of highly effective contraception is required as specified in Section 5.3.

Contraception methods with a failure rate of <1% per year when used consistently and correctly are considered highly effective. Such methods include:

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device (IUD)[2]

- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2]Contraception methods that in the context of this guidance are considered to have low user dependency.

[3]Vasectomised partner is a highly effective birth control method provided the partner is the sole sexual partner of the WOCBP trial participant and the vasectomized partner has received medical assessment of surgical success.

[4] 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 trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant

Source: (CTFG 2014)

13.1.3 Pregnancy Testing

Not applicable

13.2 Clinical Laboratory Tests

Specific analytes or parameters for clinical laboratory assessments are summarized in Table 8. Additional information is provided in the Study Reference Manual.

Table 8 Clinical Laboratory Tests

Clinical Labs for Safety [1]
[redacted]

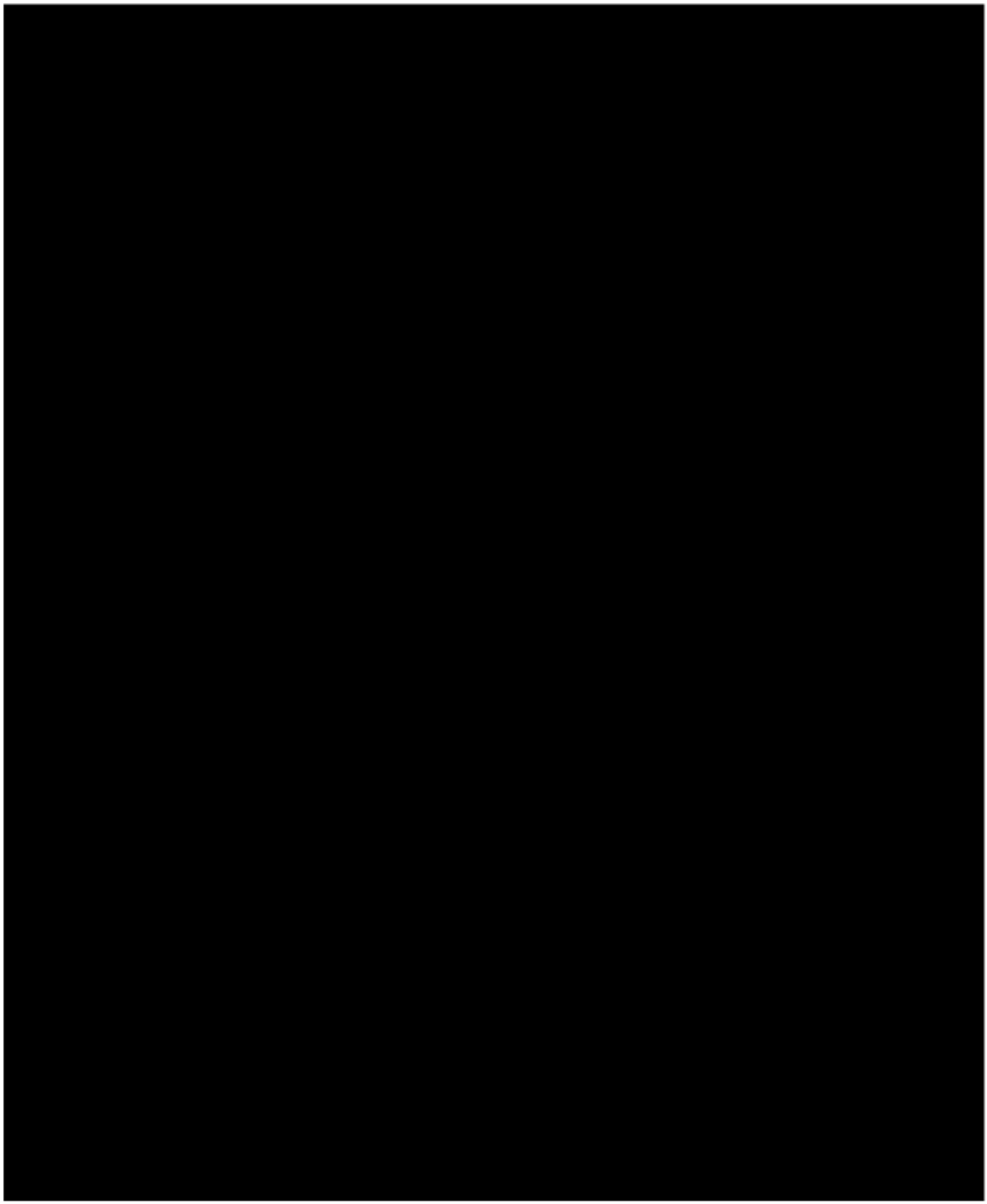
13.3 Country/Region-Specific Differences

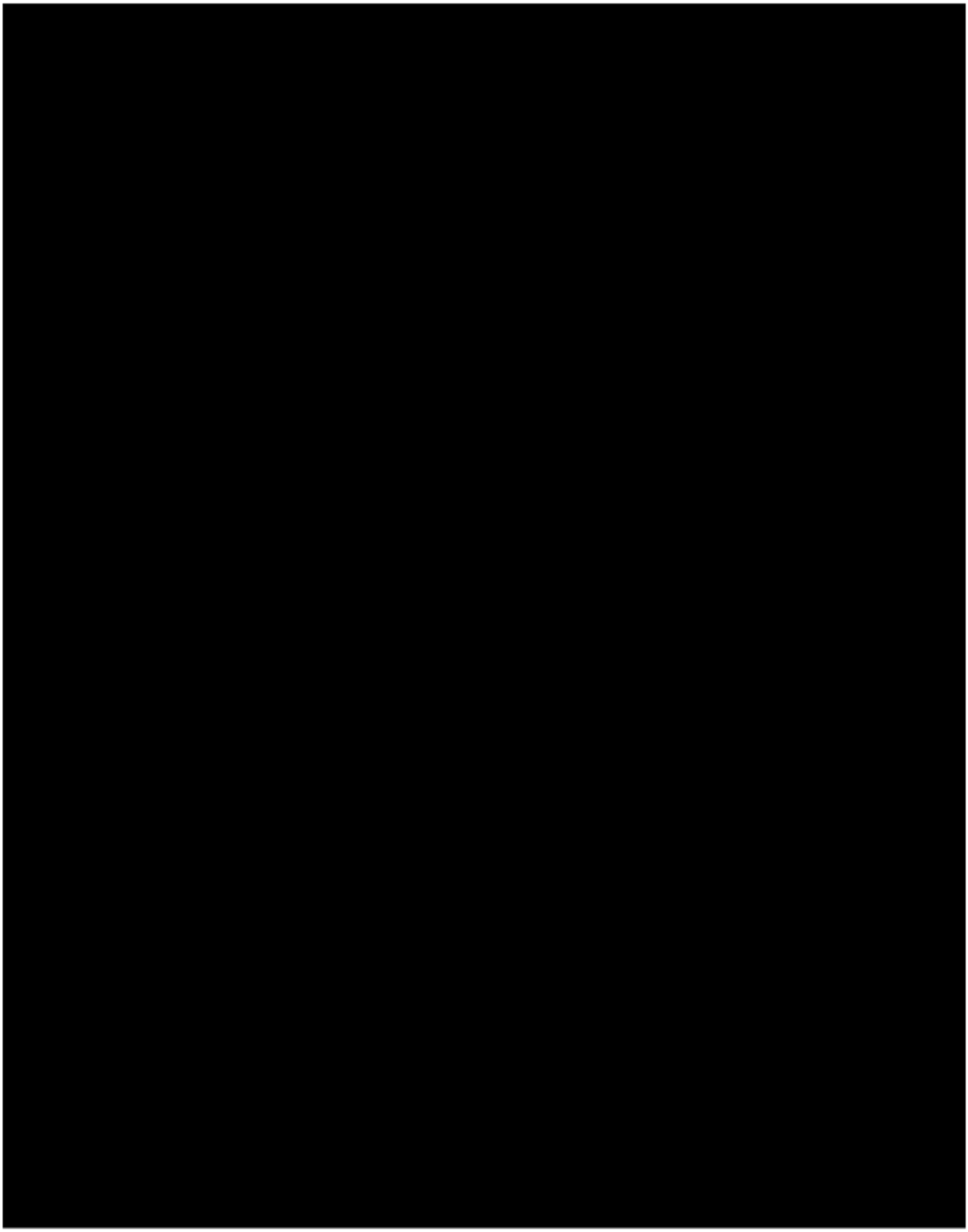
Where differences in requirements cannot be reconciled, country/region-specific amendments or addenda will be issued, if necessary, or listed below with reference to relevant protocol section.

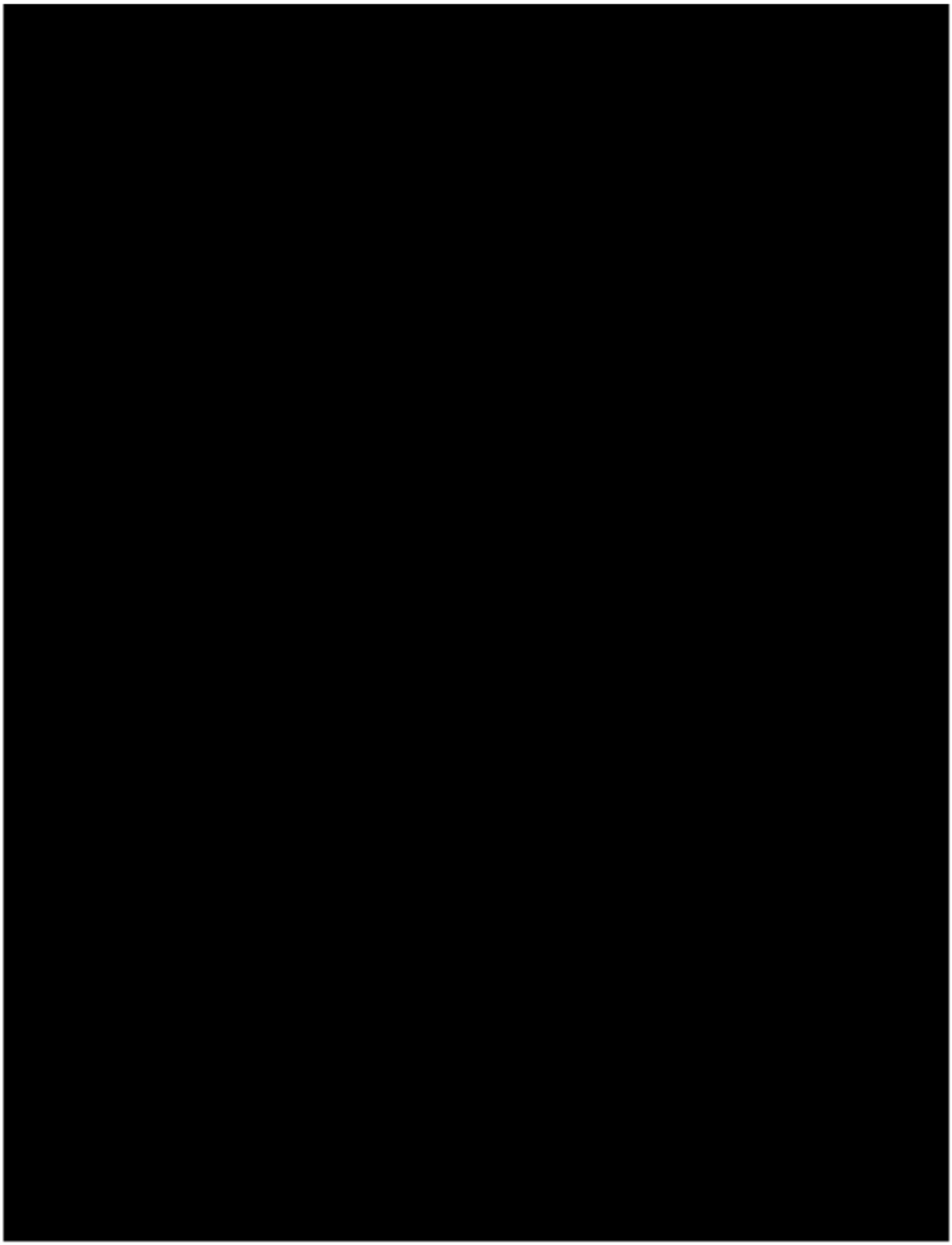
13.4 Prior Protocol Amendments

This protocol has not been previously amended.

14 APPENDIX: REFERENCES







15 APPENDIX: GLOSSARY OF TERMS

AD	Alzheimer's Disease
ADAS-Cog13	Alzheimer's Disease Assessment Scale-Cognitive 13
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASN51	ASN51 (investigational medicinal product; O-linked-β-N-acetylglucosaminidase inhibitor)
AST	Aspartate aminotransferase
CBD	Cannabidiol
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
C_{max}	Maximum concentration
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DB	Double-blind
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration, United States
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B virus surface antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IV	Intravenous
IVDR	In vitro diagnostic regulation
IWRS	Interactive web response system
LH	Luteinizing hormone
LP	Lumbar puncture
LS	Least squares
LTE	Long-term Extension

MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model for repeated measures
MMSE	Mini Mental State Exam
MRI	Magnetic resonance imaging
NFL	Neurofilament light chain
NFT	Neurofibrillary tangles
NIA-AA	National Institute on Aging and the Alzheimer's Association
OGA, O-GlcNAcase	O-linked-β-N-acetylglucosaminidase
PET	Positron emission tomography
PK	Pharmacokinetic(s)
PT	Preferred Term
QTc	Corrected QT interval (adjusted for the participant's heart rate
QTcF	QT interval corrected using Fridericia's formula
ROI	Region of interest
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reactions
SUVR	Standardized uptake value ratio
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Woman (female) of childbearing potential

16 APPENDIX: RESTRICTED MEDICATION GUIDANCE

The US Food & Drug Administration has provided guidance and examples of drugs that interact with cytochrome P-450 (CYP) enzymes and transporter systems: For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems | FDA

Briefly, drug-drug interactions can lead to changes in systemic exposure (e.g., maximum concentration (Cmax), area under the concentration time curve (AUC), average steady state concentration (Cpss) potentially resulting in adverse reactions (higher drug exposure) or loss of efficacy (lower drug exposure).

Cytochrome P-450 (CYP) enzymes are responsible for the metabolism of many drugs, and transporter systems allow for movement of many drugs across cell membranes. Thus, these enzymes and systems are often implicated in drug-drug interactions because of their effect on a drug's pharmacokinetics (e.g., drug exposure).

The list below is not a comprehensive list of all possible drugs and other substances; consult the Medical Monitor with questions as needed.

Moderate 3A4 inhibitors:

Aprepitant, ciprofloxacin, conivaptan, crizotinib, diltiazem, dronedarone, fluconazole, grapefruit juice, imatinib, isavuconazole, and verapamil

Strong Inhibitors of CYP3A4

Ceritinib, clarithromycin, cobicistat, elvitegravir, ritonavir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, paritaprevir, posaconazole, saquinavir, tipranavir, voriconazole, suboxone, telithromycin.

Moderate 2C19 inhibitors:

Cenobamate, felbamate, voriconazole

Strong Inhibitors of CYP2C19

Fluconazole, fluoxetine, fluvoxamine, and ticlopidine.

INVESTIGATOR AGREEMENT

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of ASN51 in Adults with Early Alzheimer's Disease

Protocol Number: ASN51-201

Original Protocol: Version 2.0, 07 October 2024

As an investigator, I agree to comply with all protocol specifications and ensure the safety of participants enrolled at my site. I agree to conduct the trial in accordance with applicable regulations, Institutional Review Board/Independent Ethics Committee specifications, and ICH GCP guidance. I will ensure site personnel understand their obligations in the conduct of this trial and will provide site personnel with all relevant information that becomes available during the conduct of this trial.

Principal Investigator Name:

Institution Address:

Principal Investigator Signature:

_____

Date:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

This Summary of Changes details the substantive changes to protocol ASN51-201 from the Original Protocol (1 August 2024) to Version 2 (7 October 2024). Minor changes for editorial clarifications, or for administrative corrections of typographic errors, reformatting, abbreviations or section/table re-numbering are not included in this summary. Text removed from the original version (Original Protocol) is indicated with ~~strikethrough text~~. Text added to the new version (Version 2.0) is indicated by **bold text**. Comments summarizing changes affecting large blocks of text are *italicized*.

Protocol Section	Original Text	Revised Text	Justification
1.1 Protocol Synopsis Key Eligibility Criteria		Added: •Any evidence of hepatic impairment (Child Pugh classification B and C are excluded) •Requires use of moderate or strong CYP3A4 inhibitors during trial participation •Requires use of moderate or strong CYP2C19 inhibitors during trial participation	Minor. Added clarification.
1.3 Schedule of Activities	**Tier 2 (Prescreening Period)** Plasma pTau217[d] Blood for APOE genotype	Footnote d moved: **Tier 2 (Prescreening Period)[d]** Plasma pTau217[d] Blood for APOE genotype	Minor. Added clarification to footnote d that APOE genotype may also be completed during Tier 3 of screening, so long as the result is available prior to randomization.

Protocol Section	Original Text	Revised Text	Justification
1.3 Schedule of Activities	Tier 3 (Screening Period) – added item	CDR-SB	Minor. Clarification.
1.3 Schedule of Activities	Tier 3 (Screening Period) – added item	Clinical chemistry, hematology, coagulation panel, urinalysis, urine drug screen	Minor. Added urine drug screen to screening to clarify this should be done in Tier 3
1.3 Schedule of Activities and Section 8.3.3 Electrocardiogram	Table 1; footnote f Table 2; footnote p Table 3; footnote n	ECGs should be taken supine in triplicate at approximately ~~5~~1-minute intervals. Participants should rest for at least 5 minutes in the supine position before ECGs are taken.	Minor. Clarified ECG administration instructions.
1.3 Schedule of Activities	Table 2; footnote b	Schedule all remaining visits at Day 1 visit. Visits may take more than 1 day but should take place as close to the target date as possible. Participants must complete biomarker assessments (e.g., MRI, tau PET, CSF, and plasma) before proceeding to randomization.	Minor. Emphasized and clarified randomization procedure.
1.3 Schedule of Activities and Protocol Section 8.3.5.1	For C-SSRS: Table 1; footnote g Table 2; footnote h The "Screen Version" questionnaire will be administered at Screening and at the Day 1 visit.	The "Screen Version" questionnaire will be administered at Screening ~~and at the Day 1 visit~~.	Minor. Simplify and clarify trial procedure.
1.3 Schedule of Activities & Section 8.7	Table 2; footnote l	A post-dose sample will also be obtained 1.5 to 4 hours after the participant takes the dose of trial intervention at the site and sites will record if the ~~subject~~ participant eats a full meal, as judged by the Investigator, within ± 2 hours of ~~the post-dose PK sample~~ the dose administration.	Minor. Clarified PK procedure timing in relation to food intake.

Protocol Section	Original Text	Revised Text	Justification
1.3 Schedule of Activities	Table 2; footnote m	Blood and CSF for biomarker storage and blood for pharmacogenomics will be obtained, unless collection and/or transportation of the sample is prohibited due to local regulations. At the Day 1 visit, participants must have completed the blood and CSF collection procedures before randomization.	Minor. Emphasized and clarified randomization procedure.
1.3 Schedule of Activities and Protocol Section 8.2.1	Table 2; footnote f Table 3; footnote g Cognitive and functional assessments should be performed before procedures that may be stressful for participants (e.g., MRI, PET, blood draw, or CSF sampling).	Whenever performed on the same day, c~~C~~ognitive and functional assessments (ADAS-Cog13, CDR-SB, and MMSE) are to be performed before procedures that may be stressful for participants (for example, MRI, PET, blood draw, or CSF sampling).	Minor. Clarified protocol language.
1.3 Schedule of Activities and 8.2.2.1 18F MK-6240 PET Scan	Table 2; footnote q	MK-6240 tau PET scan should be scheduled as soon as possible. Due to the potential for scheduling challenges for MK-6240 tau PET, or in the event of tracer failure, randomization may be delayed, and the screening period extended by 14 days and the Week 24 deviation window may be extended up to +21 days, with Sponsor Medical Monitor approval, though effort should be made to schedule it as close as possible to each indicated timepoint. The Day 1 visit MK-6240 tau PET scan may be performed once a subject is deemed eligible for randomization but no earlier than 21 days before randomization. At the Day 1	Minor. Emphasized and clarified randomization procedure.

Protocol Section	Original Text	Revised Text	Justification
		visit, participants must have completed their tau PET scan prior to randomization.	
5.4.1 Exclusion Criteria by Medical History	12. History of diabetes mellitus. Subjects with well-controlled diabetes mellitus and a hemoglobin A1c < 7% are permitted.	12. History of diabetes mellitus. ~~Subjects~~ Participants with well-controlled diabetes mellitus and a hemoglobin A1c < 7% are permitted.	Minor. Improved consistency of protocol language.
5.4.1 Exclusion Criteria by Medical History	22. At risk of suicide based on positive response to Question 4 or 5 on the C-SSRS at Screening.	22. ~~At risk of suicide based on positive response to Question 4 or 5 on the C-SSRS at Screening.~~ At risk of suicide based on a "yes" response to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation question 4 or 5 or any suicidal behavior assessment within 6 months before Screening, or has been hospitalized or treated for suicidal behavior within 5 years of Screening.	Minor. Improved clarity of exclusion criterion 22.
5.4.2 Exclusion Criteria by Screening Assessments	32. Liver function, any of the following: ALT ≥ 1× the ULN, AST ≥ 1× ULN, total bilirubin level (TBL) ≥ 1× ULN, or alkaline phosphatase (ALP) ≥ 1× ULN at screening.	32. Liver function, any of the following: ALT ≥ 1× the ULN, AST ≥ 1× ULN, total bilirubin level (TBL) ≥ 1× ULN, or alkaline phosphatase (ALP) ≥ 1× ULN at screening. Subjects with any degree of hepatic impairment as defined by the Child-Pugh classification are also excluded (e.g., classification B or C).	Minor. Updated liver exclusion criteria to explicitly exclude Child-Pugh classifications B and C based on FDA feedback.
5.4.2 Exclusion Criteria by Screening Assessments, Section 6.8.1, and Appendix 16	41. Prior use of a strong inhibitor of CYP3A4 within a period of 5 half-lives of randomization (refer to Appendix 16). 42. Prior use of a strong inhibitor of CYP2C19 within a period of 5 half-lives of randomization (refer to Appendix 16).	41. Prior use of a moderate or strong inhibitor of CYP3A4 within a period of 5 half-lives of randomization (refer to Appendix 16). 42. Prior use of a moderate or strong inhibitor of CYP2C19 within a period of 5 half-lives	Major. Updated list of exclusionary medications based on FDA feedback.

Protocol Section	Original Text	Revised Text	Justification
		of randomization (refer to Appendix 16). Appendix 16 updated to include: Moderate 3A4 inhibitors: Aprepitant, ciprofloxacin, conivaptan, crizotinib, diltiazem, dronedarone, fluconazole, grapefruit juice, imatinib, isavuconazole, and verapamil Moderate 2C19 inhibitors: Cenobamate, felbamate, voriconazole	
8.7 Pharmacokinetics	Participants should be contacted by telephone about 1 business day before indicated visits to remind them to bring IMP to the investigative site for administration during the visit.	Participants should be contacted by telephone about 1 business day before indicated visits to remind them to bring IMP to the investigative site for administration during the visit, and to record the time IMP is taken on the day prior to the visit.	Minor. Clarified PK procedures.
10.3 Informed Consent Process	The Investigator is responsible for obtaining written informed consent from each potential trial participant prior to the conduct of any trial procedures.	The Investigator is responsible for obtaining written informed consent from each potential trial participant and study partner prior to the conduct of any trial procedures.	Minor. No change to consent process, only updating text for clarity.
13.2 Clinical Laboratory Tests Table 8 Clinical Laboratory Tests	Follicle stimulating hormone (Screening; local laboratory)	Follicle stimulating hormone (Screening; local or central laboratory)	Minor. Clarification of laboratory procedure.

Protocol Section	Original Text	Revised Text	Justification
13.2 Clinical Laboratory Tests **Table 8 Clinical Laboratory Tests**	Collection of CSF in polypropylene tubes. Cell count, protein, glucose.	Collection of CSF in polypropylene tubes. Cell count (white blood cells with differential and red blood cells), protein, glucose.	Minor. Clarification of laboratory testing.
Investigator Signature Page	~~A Phase 2, Double Blind, Randomized, Placebo-Controlled Dose-ranging Safety Trial of ASN51 in Adults with Early Alzheimer's Disease~~	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of ASN51 in Adults with Early Alzheimer's Disease	Minor. Corrected protocol title on investigator signature page.