Phase II Study to Assess the Safety, Tolerability, and Target Engagement of AMX0035, a Fixed Combination of Sodium Phenylbutyrate and Tauroursodeoxycholic Acid for the Treatment of Alzheimer's Disease

[redacted]

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By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

[redacted]

5/7/2021

Date

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5/8/2021

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[redacted]

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5/7/2021

Date

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	10 Oct 2020	[redacted]	not applicable—first version
0.2	2 Nov 2020	[redacted]	add clarification to primary analysis and CSF markers gating;
0.3	3 Dec 2020	[redacted]	Add clairification to primary analysis and modify patient population definitions

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1 Abbreviations

AE	Adverse Event/Adverse Experience
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ALS	Amyotrophic Lateral Sclerosis
BOLD	Blood Oxygen-Level Dependent Imaging
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DSRS	Dementia Severity Rating Scale
eCRF	Electronic Case Report Form
FAQ	Functional Activities Questionnaire
FDA	Food and Drug Administration
g	Gram
GST	Global Statistical Test
IL	Interleukin
ITT	Intention to Treat
LP	Lumbar Puncture
MADCOMS	Mild/Moderate AD Composite Scale
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MoCA	Montreal – Cognitive Assessment
MRI	Magnetic Resonance Imaging
N	Number (typically refers to subjects)
NfL	Neurofilament Light Chain
Ng	Neurogranin
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory Questionnaire
PB	Sodium Phenylbutyrate
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol

SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SI	Site Investigator
SOP	Standard Operating Procedure
TUDCA	Tauroursodeoxycholic Acid
US	United States
vMRI	Volumetric Magnetic Resonance Imaging

Table 1. Schedule of Assessments

	Screening	Baseline[1]	Week 1 Phone Call	Week 6[15]	Week 12[16]	Week 18[15]	Week 24[17]/Early Discontinuation[18]	Final Follow-Up Call[14]
	-28 Days	Day 0 +5 Days	Day 7 ±1 Days	Day 42 ±14 Days	Day 84 ±28 Days	Day 126 ±14 Days	Day 168 ±28 Days	Last Dose of IP +14 ±5 Days
Written Informed consent	X							
Inclusion/Exclusion Review	X	X						
Randomization[2]		X						
Medical History/Demographics	X							
AD Diagnosis History	X							
Montreal - Cognitive Assessment (MoCA)	X			X		X	X	
DSRS		X			X		X	
Geriatric Depression Scale	X							
Vital Signs[3]	X	X			X		X	
FAQ		X			X		X	
Physical Exam including Height and Weight[4]	X						X	
Neurology Exam[5]	X						X	
Safety labs[6]	X				X		X	
12-Lead ECG (Electrocardiogram)	X				X		X	

	Screening	Baseline[1]	Week 1 Phone Call	Week 6[15]	Week 12[16]	Week 18[15]	Week 24[17]/Early Discontinuation[18]	Final Follow-Up Call[14]
	-28 Days	Day 0 +5 Days	Day 7 ±1 Days	Day 42 ±14 Days	Day 84 ±28 Days	Day 126 ±14 Days	Day 168 ±28 Days	Last Dose of IP +14 ±5 Days
Neuropsychiatric Inventory Questionnaire (NPI-Q)	X[7]				X		X	
ADAS-Cog		X			X		X	
MRI Assessment[8]	X						X	
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X
Dispense Study Drug[9]		X		X	X	X		
Drug Accountability/Compliance			X[10]	X	X	X	X	
Suicide Rating Scale (C-SSRS)[11]	X	X		X	X	X	X	
Blood draw for biomarker analysis		X			X		X	
Lumbar puncture/CSF draw for biomarkers[12]	X						X	
Blood draw for pharmacokinetics[13]					X		X	
Blood draw for genetic analysis		X						

[1]The Baseline Visit can be completed any time after the screening so long as all eligibility criteria are met and occur no more than 28 +5 days after the Screening Visit.

[2]Randomization should occur at the Baseline Visit. Randomization will entail entering a subject's kit number into the electronic data capture system.

[3]Vital signs include systolic and diastolic pressure in mmHg, respiratory rate/minute, heart rate/minute and temperature.

[4]Height is only recorded once at the Screening Visit.

[5]The standard Neurological Exam will be used for all subjects.

[6]Safety labs include Hematology (CBC with differential), Complete Chemistry Panel, Liver Function Tests, B12 and TSH (at Screening Visit only) and Urinalysis.

[7] The NPI-Q Test can be performed either at the screening or baseline visit
[8]The MRI assessment can be completed anytime between the Screening and up to 7 days prior to the Baseline Visit and will have a clinical read done locally.

[9]First dose of study drug will be administered in clinic after ALL Baseline Visit procedures are completed.

[10]Notify subjects of increase from one sachet per day to two sachets per day

[11]C-SSRS Screening Version to be completed at Screening Visit only. C-SSRS Since Last Visit version to be completed at all other visits.

[12]The first LP can be completed anytime between the Screening and up to 7 days prior to the Baseline Visit.

[13]Take a single PK plasma sample on Visits 12 and 24 (same time as lumbar puncture). A PK sample will not be taken on subjects completing the Early Discontinuation Visit if the subject discontinued study drug more than 48 hours before the visit.

[14]The Final Follow-Up Call is to occur 14 ± 5 days after the participant's last dose of study drug. For participants who discontinue treatment early, the Final Follow-Up Call is not required if the Early Discontinuation visit occurs 14 ± 5 days after the last dose of study drug.

[15]To the extent possible, the Week 6 and Week 18 visits may be done remotely. If the visit is done remotely, Drug Accountability/Compliance will occur at the next in-person clinic visit.

[16]It is preferred that the Week 12 visit be conducted at the site with the participant physically present. If it is not possible to complete an in-person Week 12 visit at the site, the safety assessments below must be completed by Week 16/Day 112 for the subject to remain on study drug. Sites may make alternative arrangements to complete these assessments per institutional and IRB policy.

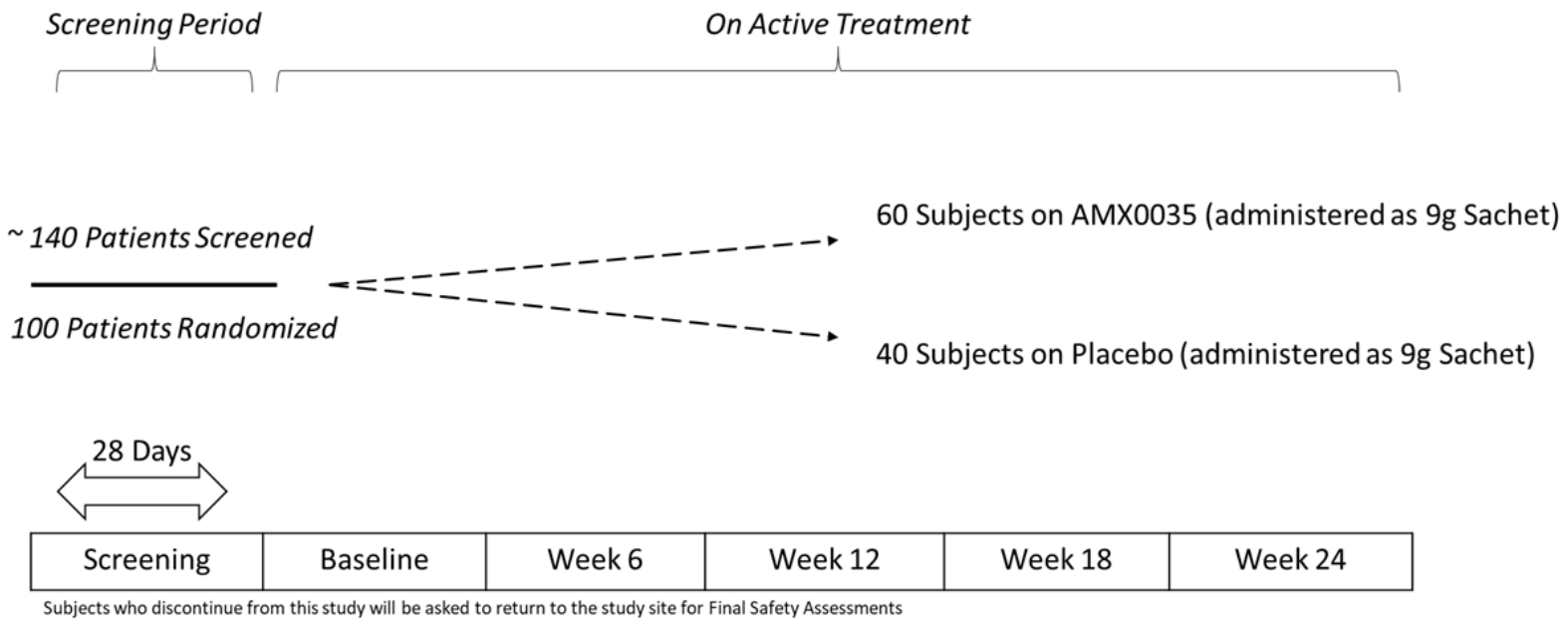
- ECG
- Safety Labs: Hematology (Complete Blood Count with Differential), Complete Chemistry Panel, Liver Function Tests, and Urinalysis

- Vital Signs
- C-SSRS

[17] The window for the Week 24 visit is Day 168 ± 28 days. However, if COVID-19 related restrictions (e.g., site closure, travel restrictions) make it impossible to conduct an in-person clinic visit during the specified window, then any assessment that can be performed remotely should be completed as an unscheduled visit during the Week 24 window. The actual Week 24 visit, with all of the assessments indicated on the SOA, may be postponed for up to 12 weeks and treatment extended. The maximum duration a subject may be on IP is 40 weeks. Safety checks (i.e., ECG, safety labs, vital signs, and C-SSRS) must be completed, at minimum, every 16 weeks/112 days. If safety assessments are performed so that the Week 24 visit may be postponed, the assessments should be documented as an unscheduled visit.

[18]If possible, an Early Discontinuation visit should be done within 14 days of the last dose of IP (i.e., last dose of IP + 14 days). The MRI and lumbar puncture may be done as soon as is practical and, if possible, within 60 days of the last dose of IP (i.e., last dose of IP + 60 days).

Figure 1. Study workflow



2 Introduction

Alzheimer's disease is characterized by the loss of neurons and synapses in the cerebral cortex and atrophy in the temporal and parietal lobes. Abnormal aggregates of amyloid plaques and neurofibrillary tangles are the primary histopathological findings of AD and are the target of many clinical trials. However, recent studies suggest that amyloid reduction may be less able to halt pathology after AD has progressed beyond the stage of mild cognitive impairment (MCI). At this stage, neuronal death and inflammatory pathways may contribute to disease progression to a greater degree than amyloid or tau. This suggests that there may be patient sub-groups that may not respond to amyloid-targeted therapies, yet may benefit from therapies targeting cell death and inflammation.

AMX0035 is a combination of two compounds, Sodium Phenylbutyrate (PB) and Tauroursodeoxycholic Acid (TUDCA), that target the unfolded protein response (UPR) and bioenergetics stress, respectively. Both compounds are expected to cross the blood-brain-barrier at therapeutic levels based on observed CNS target engagement observed in previous *in vivo* studies[3,4,7,11,14] and are hypothesized to prevent neuronal death through distinct pathways. Synergistic effect of these compounds has been found in preclinical models.

3 Trial Overview

3.1 Design

This is a 24-week, phase II, longitudinal, multi-center, randomized, double-blind, placebo-controlled trial to assess safety and tolerability of a fixed-dose combination of AMX0035 in subjects with MCI or dementia due to AD. Approximately 100 subjects will be randomized 3:2 (active:placebo) to oral, twice daily sachet of active combination (TUDCA/PB) or placebo.

3.2 Study Objectives

3.2.1 Primary Objectives

1. To compare the safety and tolerability of a fixed-dose combination of AMX0035 (a TUDCA/PB combination) versus placebo in subjects with MCI (high or intermediate likelihood due to AD) or dementia due to AD over an approximate 24-week treatment period;
2. To determine the effects of AMX0035 treatment on AD progression as measured by a global statistical test (GST)

3.2.2 Secondary Objectives

1. To determine the effects of AMX0035 treatment on whole brain and regional brain atrophy, as assessed by volumetric Magnetic Resonance Imaging (vMRI);
2. To measure the effects of treatment on functional MRI measures including connectivity with resting state BOLD;
3. To assess the impact of AMX0035 on clinical symptoms as measured by ADAS-Cog, DSRS, FAQ, and additional clinical outcomes;

4. To assess the effect of AMX0035 on measures of neuropsychiatric symptoms, as assessed by the Neuropsychiatric Inventory Questionnaire (NPI-Q)

The primary estimand is the effect of treatment as measured by a change from baseline in GST (comprised of Mild/Moderate AD Composite Scale (MADCOMS), FAQ, and hippocampal volume) estimated at 24 weeks relative to placebo in individuals with MCI (high or intermediate likelihood due to AD) or dementia due to AD. The study population for the primary estimand will be the intent to treat population.

3.3 Sample Size Determination

A sample size of approximately 100 randomized subjects was chosen based on feasibility and is not based solely in statistical considerations. Subjects will be randomized in a ratio of 3:2 (active versus placebo). In order to maximize study power for evaluation of efficacy end-points, a GST will be used. The GST will be a combination of 3 change-from-baseline to end-of-study endpoints (univariate components):

- Cognition (ADAS-Cog)
- Functional Activities Questionnaire (FAQ)
- Total Hippocampal Brain Volume

For purposes of power calculations, GSTs can be characterized based on the assumed effect sizes of each of the 3 component endpoints and the correlations between each of the 3 pairs of component endpoints.

We assume a correlation of 0.4 between the cognitive and FAQ component endpoints and a correlation of 0.2 between the total hippocampal volume component endpoint and each of the other two components endpoints (i.e., the cognitive component endpoint and the FAQ component endpoint), based upon historical analyses. By using 50% statistical power and the assumed effect sizes as inputs, we can obtain the "expected p-value" for 2 selected combinations of component endpoints of the composite. We do this in 2 stages, first for the combination of ADAS-Cog and FAQ component endpoints, which have expected p-values of 0.09409 and 0.20184, respectively, resulting in a 2-component expected p-value of 0.077583. Then we combine the 2-component expected p-value with the expected p-value for Total Hippocampal Brain Volume (0.20184), to get a GST expected p-value of 0.049756.

Each of the 3 component endpoints may have a different sensitivity with respect to detecting change over time. The sensitivity is quantified using the Mean-to-Standard Deviation Ratio (MSDR), which is calculated by dividing the mean of the change-from-baseline score by the standard deviation of the change-from-baseline score. For change-from-baseline to 6 months,

we assume the MSDR values for ADAS-Cog, FAQ, Total Hippocampal Volume are 0.8, 0.6, and 0.6, respectively. We assume a 60% value for Percent of Placebo Effect (i.e., the decline for the active treatment group is only 40% of the decline of the Placebo group). This corresponds to effect size (assumed treatment difference divided by the common standard deviation) values of 0.48 for the Cognitive Endpoint, 0.36 for the FAQ endpoint, and 0.36 for the Total Hippocampal Brain Volume endpoint. Under these assumptions the resulting GST p-value is 0.049756.

Using 100 randomized subjects (assuming either no subject dropout so that there are 100 completers, or that imputation appropriately accounts for subject dropout), 50% power, a randomization ratio of 1:1, gives an effect size (corresponding to the use of the GST) of 0.566; this indicates that that under these assumptions use of the GST is equivalent to using a single component test statistic with an effect size of 0.566 (rather than the assumed effect sizes of 0.48 for ADAS-Cog, 0.36 for FAQ, and 0.36 for Total Hippocampal Brain Volume). Another way to interpret this is that using of the GST, corresponding to an assumed effect size of 0.566 for a single component endpoint, and using $\alpha = 0.05$ results in a power of approximately 50% (50.1%). So, when the individual components of the GST are in the same direction (and in favor of the active treatment group versus placebo), then use of a GST generally provides more power than use of a single component.

Although the power calculations (Table 2) show 80% power for an assumed Percent of Placebo Effect value of 85%, a Percent of Placebo Effect value as small as 50% or 60% would still be clinically relevant and would be an encouraging indication for moving forward into a new study. As described previously, a Percent of Placebo Effect value of 60% corresponds to GST p-value of approximately 0.05 (0.049756, 2-sided), an effect size of 0.566, and a power of approximately 50%. A GST p-value of 0.10 (2-sided) would be an observed trend that would still be suggestive of a signal indicating that moving forward into a new study would be appropriate. This corresponds to Percent of Placebo Effect value of just under 50%: a Percent of Placebo Effect value of 50% corresponds to GST p-value of approximately 0.095 (0.09477, 2-sided), an effect size of 0.479, and a power of approximately 38% at a 2-sided alpha=0.05 level.

Some additional examples of the GST under various assumed Percent of Placebo Effect values and corresponding effect sizes (and using the pairwise correlations of 0.4, 0.2, and 0.2 described previously) are given below, along with the examples described previously. (Note that a Percent of Placebo effect value of 0% means that active treatment declines as much as Placebo, a value of 50% means that active treatment declines half as much as Placebo, and a value of 100% means that the active treatment doesn't decline at all over the 6-month treatment period.)

We included conservative estimates of power calculations based on ADAS-Cog. The GST implemented in the analysis will incorporate MADCOMS, which has been previously shown to be more sensitive to change in mild to moderate populations (S Hendrix ADPD 2021).

Table 2. Power of Global Test Statistic for total sample sizes of 50, 76, and 100 subjects for Protocol AMX8000 using a 3:2 randomization ratio

Percent of Placebo Effect	Cog. Effect Size	FAQ Effect Size	Total Hipp. Brain Volume Effect Size	Global Test Statistic Effect Size	Global Test Statistic Power (%) 50 Subjects Total	Global Test Statistic Power (%) 76 Subjects Total	Global Test Statistic Power (%) 100 Subjects Total
50%	0.40	0.30	0.30	0.479	36.9	52.2	64.2
60%	0.48	0.36	0.36	0.566	48.5	66.3	78.4
70%	0.56	0.42	0.42	0.651	60.0	78.2	88.4
80%	0.64	0.48	0.48	0.754	72.6	88.7	95.5
85%	0.68	0.51	0.51	0.803	77.8	92.2	97.4
90%	0.72	0.54	0.54	0.852	82.4	94.8	98.5
100%	0.80	0.60	0.60	0.951	89.7	97.9	99.6

3.4 Blinding and Unblinding

Once all eligibility criteria for the study have been met, the subject will be randomized by the biostatistical team with an allocation ratio of 3:2 by a computer-generated random sequence at the baseline visit. All participants and individuals employed by Amylyx or [redacted] will be blinded to treatment groups until database unlock. After database lock, [redacted] statisticians will request the treatment codes, the study will be unblinded and the statistical analysis will be conducted.

3.5 Study Drug Administration

Prepackaged AMX0035 sachets will be self-administered daily for 24 weeks. AMX0035 dose is 3g PG and 1g TUDCA (active) or matching placebo. Individuals will take a single sachet daily for the first week. Dosage will be increased to 2 sachets daily after 1 week (if tolerated) for the duration of study participation.

4 Patient Chronology

Study days will be numbered from Day 1, the first day of study medication intake.The duration of events, such as the duration of treatment, will be taken as the end date minus the start date (Day 1), plus 1.

5 General Conditions for the Final Analysis

5.1 Definitions

Safety endpoints representing the change from baseline at a particular visit will be defined as the result at the visit minus the last non-missing result prior to the first dose of study medication. Should a baseline value be missing, then the corresponding screening value, if available, may be used. Efficacy endpoints representing the change from baseline at a

particular visit will be defined as the result at the visit minus the average of the non-missing results collected prior to the first dose of study medication. Change from baseline will be missing for data collected prior to the first dose of study medication. Patients with a missing score for either baseline or the applicable visit will have a missing value for the change from baseline at that visit.

Whether an improvement is represented by a positive or negative change from baseline will depend on the endpoint.

5.2 General Considerations for the Final Analysis

All analyses will be carried out in SAS version 9.3 or R version 3.4 or higher.

Visits will be designated as Screening, Baseline/Week 1, Week 6, etc as defined in Table 1.

Summaries will be shown with columns for each treatment group as well as a column for all patients in the study and applicable population. The number of subjects in the treatment group and population will be shown in the column header. Continuous data will be summarized with the number of non-missing values and their mean, standard deviation, median, minimum and maximum. Categorical data will be summarized as the count and percentage of distinct patients with each value. Unless noted otherwise and for a given analysis population (see section 6.3 for definitions), the denominator will be the total number of subjects in this analysis population who belong to the treatment group. Summaries by visit will include only regularly scheduled visits.

All data in the clinical database will be listed with the exception of prompt, drug label or data review / investigator signature pages. Listings will not be subset by analysis population. Listings will generally be sorted by patient number, parameter and visit date. Unscheduled visits will be listed, but they will generally not be summarized.

If it happens that no patients qualify for a display the display will be produced with a note that "No patients qualify for the display." For example, if there are no deaths then the applicable displays will be so noted.

Further details appear in the mock display document.

For safety summaries, the last pre-randomization measurement is defined as the baseline value. For efficacy measures baseline is defined as the last pre-randomization measurement.

Visit windowing will be applied for analyses which use visit categories instead of actual number of days relative to dosing for each assessment. For categorical visit summaries, all visits including early termination assessments and unscheduled visits will be included with the closest scheduled post-baseline visit that includes the efficacy or safety assessment, based on number of days since Day 0. If an early termination visit and a regular visit (other than baseline) both fall within the same visit window, any non-missing efficacy assessments will be averaged, and a worst-case severity approach will be used for safety data.

If partial dates are recorded for efficacy or safety outcomes, then partially missing start/beginning date (e.g. AE/Concomitant medication start date) will fill in the missing month with January and missing day with 1. For example, if month and day were both missing, then the date would be filled in with January 1st. Partially missing end/finishing date (e.g. AE/Concomitant medication end date) will be filled in with December and missing day with

the last day of the month. For example, if month and day were both missing, then the date would be filled in with December 31st. For other outcomes (e.g. date of vital signs collection) fill in missing month with June (middle month) and missing day with the middle day of the month. For example, if month and day were both missing, then the value would be filled in with June 15th.

Days will be converted to weeks by dividing by seven. Days will be converted to months by dividing by 30.417. Days will be converted to years by dividing by 365.25. All data collected during the study will be analyzed and reported unless stated otherwise.

5.3 Interim Analysis

No interim analysis of the data will be conducted.

5.4 Changes to Statistical Analysis

The statistical analysis plan does not deviate significantly from the protocol.

5.5 Analysis Populations/Sets

5.5.1 All Patients Population

The All Patients Population is defined as patients with any record in the database. This population includes both screening and randomized subjects. Population will be utilized for descriptive patient counts that include screening subjects.

5.5.2 Intent-to-Treat (ITT) Population

All randomized subjects will be included in the ITT population and will be analyzed as randomized. The ITT population will be analyzed for efficacy in place of the mITT as per the recent FDA suggestion.

5.5.3 Per Protocol (PP) Population

The PP Population is defined as those ITT patients who took the study medication for 20 weeks or more and did not have any major protocol deviations. For programming purposes, they will be identified as having 80% compliance estimated from study drug return over the 24 week treatment period and having no major protocol violation as identified separately by the Sponsor Medical Director prior to database lock. Analyses of the PP population will be analyzed as treated.

5.5.4 Safety Population

The safety population includes all randomized subjects who received at least 1 dose of study medication. Subjects in the safety population will be analyzed as treated.

5.6 Estimands, Intercurrent Events, and Missing Data

Summary of primary estimand:

In individuals with MCI (high or intermediate likelihood due to AD) or dementia due to AD, what is the effect of treatment taken for 24 weeks (estimated from the model) relative to placebo during the double-blind phase, in the protocol-defined ITT study population as measured by a GST that encompasses MADCOMS, FAQ, and hippocampal volume.

1. Objective

   An estimate of efficacy which would potentially be supportive of proof of concept

2. Estimand

A. The population is the ITT population as defined by the protocol's inclusion and exclusion criteria.

B. Efficacy is measured by the estimated change from baseline at 24 weeks in the primary endpoint (GST)

C. The treatment evaluated is the randomized treatment as it was assigned to study subjects. All types of intercurrent events are incorporated using a treatment policy strategy, which evaluates the randomized treatment as taken including missed or modified doses, drug discontinuation, and concurrent treatments. Deaths are not expected during the 24 week study.

D. The mean change from baseline between treatment and control arms on the primary endpoint will be estimated at 24 weeks. A significant difference at a familywise error rate of 5% will be required for success. However we will consider a trending association ($P<0.1$) as proof of concept given the small sample size of the study.

3. Primary estimator and missing data.

   The estimator is a continuous time MMRM using all available assessments. Due to the small sample size the model will be optimized by implementation of two composite covariates that account for multiple baseline covariates in one variable. The composite covariate will be derived from blinded data and generated using the baseline model covariates (excluding treatment and visit) or the baseline model covariates* time interactions. The composite covariates will be included as a covariate in the model.

   Item scores that compose the GST for individuals that have right censored missing values and at least one baseline visit will be carried forward using LZCF. If an individual is missing all post-baseline data, the z-score of the population baseline values will be used to estimate the LZCF within treatment groups for post-baseline visits. Interim visits for total hippocampal volume, which was assessed at baseline and 24 weeks, will be imputed using straight line imputation at the observed or scheduled visit timepoints. Straight line imputation will also be performed for items that compose the GST (MADCOMS and FAQ) for timepoints with intermittent missing values (i.e. flanked by timepoints with data collected). The 24 week estimate will be drawn from the MMRM model using the data imputed as described.

   LZCF assumes that subjects will follow the same trajectory after dropping out of the study, conditional on the model covariates as listed in Section 7.5.1. However, if subjects tend to preferentially drop out due to study drug related events, it is possible that their post-dropout trajectory may differ from their pre-dropout trajectory. In this

case the above specified assumption may not hold. A sensitivity analyses is proposed to assess this scenario.

4. Sensitivity analyses and missing data.

   To assess the effect of LZCF on the primary outcome, the MMRM will be repeated without LZCF imputation and mean differences assessed. The primary analysis will incorporate hippocampal volume quantitation from cross-sectional data to meet the ITT population requirements. A separate sensitivity analysis using the subset of data with longitudinal pairs will also be performed.

5.7 Data Review

Classification of deviations from the protocol as minor or major, and decisions regarding patient population assignments will be decided on a case-by-case basis without knowledge of the treatment assigned and before the database lock in a blinded data review meeting. After database lock, the responsible statistician will request the treatment codes, the study will be unblinded, and the statistical analysis will be conducted.

5.8 Missing Data

Patients who drop out will have all available post-baseline data included in the analysis, unless otherwise specified. Patients that lack information at a visit due to early termination, etc will be imputed using LZCF for efficacy analyses. LZCF allows imputation of the data such that individual trajectory carries on relative to the mean and standard deviation at each visit. For individuals with only baseline data, baseline z-scores will be used to calculate LZCF for post-baseline visits within treatment groups. All patients will appear in each listing. Patients Excluded from One or More Analysis Sets (Listing 16.1.4), General Comments (Listing 16.1.7), Serious AEs (Listing 16.3.1.2), AEs Leading to Discontinuation or Death (Listing 16.3.2), and Clinically Significant Laboratory Abnormalities (Listing 16.3.4). Patients with no applicable data will be listed with “No Data” on the line.

Additionally, patients with intermittant missing data will have values imputed using straight line imputation. Right censored data will be imputed using LZCF. In the event that a total score is missing individual items, LZCF or straight line imputation will be performed at the item level to fill in missing values prior to calculating total scores.

6 Study Conduct

6.1 Treatment Assignments

Upon locking the database the study will be unblinded. Blinded reconciliation of demographic elements between this list and the clinical database will already have taken place. The treatment assignment will be given to each patient and 100% verified.

6.2 Enrollment, Demographics, and Baseline Characteristics

A summary table will be provided for the All Patients Population to show the study timelines: the earliest and latest date of screening visit, of study drug intake, and study participation as well as the duration in days of screening, treatment and study participation.

A summary table will be provided for the Safety Population to summarize demographics, i.e. age, gender, race, height and weight at baseline. The table will be repeated for the ITT and PP Populations. The equality between treatment groups for each of these parameters will be tested with a t-test or Fisher's exact test, as appropriate.

The supportive listings will present all data on the Informed Consent / Demographics CRF page. The listings of disposition, drug dispensing and return, and vital signs also partly support these tables.

6.3 Patient Disposition and Protocol Deviations

A summary table will be provided for the All Patients Population to display the number of subjects randomized, Safety Population, ITT Population, and patients who completed or discontinued the study. Listings will be provided for the different reasons for screen failure, discontinuation, and exclusion from the analysis populations. Reasons for discontinuation will be taken from the End of Study form. Reasons for exclusion from the PP Population will be taken from the PP source documentation mentioned in Section 5.5.3.

A summary table will be provided for all randomized patients to include those with at least one deviation. Major deviations as reported on corresponding eCRF will be summarized; within each classification the count and percent of each category that appears on the CRF will be displayed.

Supportive listings will present all information on the Study Completion / Early Termination CRF page and the Protocol Deviations page. Another supportive listing will display patients excluded from any analysis population along with the reason(s) for exclusion.

6.4 Extent of Exposure to Study Drug

A summary table will be provided for the Safety Population stratified by treatment group to summarize the duration of treatment, total dose received, average dose per day and compliance. The count and percentage of subjects with compliance below 80% and above 110% will be provided as an assessment of under/overdosing.

The supportive listing will present all data on the Drug Dispensing and Return CRF page.

6.5 Medical History

Abnormal medical history findings are recorded by system. Patients with no abnormal medical history have a No at the top of the page and have the rest of the page blank. Patients with some abnormal history but also some normal systems have N/A for the normal systems.

Findings are coded with the Medical Dictionary for Regulatory Affairs (MedDRA). The version number will be shown as a footnote in the displays. A listing will be provided of these data and will include all patients in the study. A summary table will be provided to

show the count and percentage of patients with abnormal medical history by system organ class and preferred term. Patients will be counted at most once per term.

6.6 General Comments

A listing will be provided of all general comments recorded on the corresponding CRF page.

Any deviations from the SAP will be described.

7 Efficacy Analyses

All efficacy endpoints will be characterized for association response to treatment over time and effect size for the purposes of designing an efficacy study using the ITT and Per Protocol populations.

7.1.1 Primary Endpoints

1) To assess the impact of AMX0035 on AD progression by assessing the performance of multiple outcome measures using a global statistical test (GST) (MADCOMS, FAQ, hippocampal volume (MRI)) for change from baseline to 24 weeks.

7.1.2 Secondary Endpoints (listed in hierarchical order)

1. To assess the impact of AMX0035 on hippocampal volume.

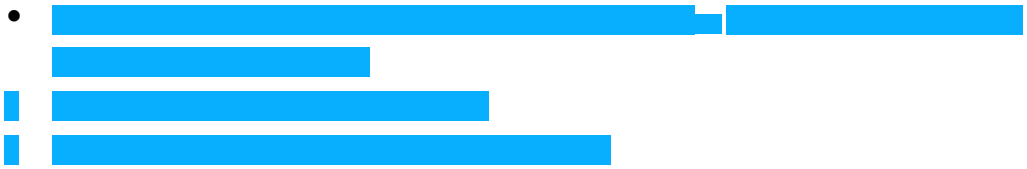
To assess the impact of AMX0035 on clinical symptoms as measured by:

2. MADCOMS
3. ADAS-Cog14
4. FAQ
5. DSRS
6. MoCA
7. Neuropsychiatric Inventory Questionnaire (NPI-Q)

7.1.3 Biomarker Endpoints

To determine the effects of AMX0035 treatment on:

1. whole brain volume
2. ventricular volume
3. functional MRI measures including connectivity with resting state BOLD;
4. cerebrospinal fluid (CSF) and plasma biochemical markers, including:



- [redacted]
- [redacted]

Primary Efficacy Endpoints

7.2.1 Global Statistical Test

A GST allows assessment of a global change in disease status/trajectory by standardizing and then combining measures. The GST will be a combination of 3 change from baseline to end of study endpoints (MADCOMS, FAQ, and total hippocampal brain volume). The GST will be calculated for each subject as a mean score across the three component endpoints. This mean score will be analyzed as the primary efficacy outcome variable.

7.2.2 MADCOMS

ADAS-Cog 14 is not specifically targeted to the mild/moderate stage of AD. A mild/moderate AD composite scale (MADCOMS) was previously optimized for the two distinct groups, mild AD (baseline MMSE 20-26) and moderate AD (baseline MMSE 14-19). The weighted composite was derived using PLS regression from ADAS-Cog, MMSE, and CDR individual items (S.Hendrix ADPD 2021).

Moderate MADCOM=

$$\begin{aligned} &Comprehension * 0.36390157 + Word\ Finding * 0.10931155 \\ &+ Ideational\ Praxis * 0.42535667 + Naming\ Objects \\ &* 0.65626894 + Word\ Recognition * 0.05159097 \\ &+ Word\ Recall * 1.0698506 + Spoken\ Language \\ &* 0.3019936 + Home\ and\ Hobbies * 0.66529282 + Memory \\ &* 0.12277257 - Orientation\ to\ Place * 0.23001218 \\ &- Spell\ Backward * 0.07980965 - Language\ and\ Praxis \\ &* 0.18954955 \end{aligned}$$

Mild MADCOM=

$$\begin{aligned} &Word\ Finding * 0.39065568 + Word\ Recall * 1.14084544 \\ &+ Spoken\ Language * 1.09895590 + Personal\ Care \\ &* 0.60865765 + Community\ Affairs * 0.15706995 \\ &+ Judgment * 1.40920029 - Orientation\ to\ Time \\ &* 0.27596627 \end{aligned}$$

The current study collected DSRS (equivalent to CDR) and MoCA (equivalent to MMSE). The equivalent DSRS and MoCA test items were scaled to the MMSE or CDR test range and used to make MADCOMS.

MMSE to MoCA conversion:

MMSE Domain	MoCA question(s)	scale
Orientation to Time	17-20	5/4
Orientation to Place	21-22	5/2
Attention and Calculation	10	5/3
Recall	14	3/5
Naming	6	2/3
Repetition	11	1/2
Commands	9	3/1
Reading	13	1/2
Drawing	2	1

CDR to DSRS conversion:

CDR Domain	DSRS question(s)
Memory	1
Orientation	4-5
Judgement and Problem Solving	6
Community Affairs	7
Home and Hobbies	8
Personal Care	9 & 11

DSRS values were converted to CDR scales by dividing the sum of the DSRS questions that make up the equivalent CDR domain score by the max score for those questions. Memory, orientation, judgement and problem solving, community affairs, as well as home and hobbies are multiplied by 4 to create 5 categories. That are assigned to 0,0.5,1,2, or 3 by their rank value. Personal care scores are multiplied by 3 to create 4 categories that are assigned to 0,1,2, or 3 by their rank value.

7.2.3 FAQ

The FAQ, is a secondary endpoint, however included here due to inclusion in the GST. FAQ is a brief informant-administered rating scale used to determine a subjects' level of functional independence when performing a range of instrumental activities of daily living (IADLs), with repeat assessments useful for monitoring performance in these areas over time[47]. The FAQ total score (ranging from 0-30) reflects the sum of ordinal ratings (0 =

fully independent, 1 = has difficulty but does by self, 2 = requires assistance, and 3 = dependent) across ten items assessing a variety of functional activities (i.e., preparing a balanced meal, financial management skills, and shopping), with higher scores indicating increasing levels of dependence. For activities not normally undertaken by a person, a score of 1 is assigned if the informant believes the subject would be unable to complete the task if required, or a score of 0 is assigned if the informant believes the subject could successfully carry out the task if needed. Overall, the FAQ is a sensitive marker of functional impairment among individuals with varying dementia severity[43], and has been shown to differentiate mild cognitive impairment from early Alzheimer's Disease with 80% sensitivity and 87% specificity[49]. The FAQ demonstrates high reliability (exceeding 0.90), takes about 5 minutes to complete, and requires limited rater training to administer[47]. The FAQ will be administered at the Baseline, Week 12, and Week 24/Early Discontinuation Visits.

7.2.4 Total Hippocampal Brain Volume (volumetric MRI)

Whole brain volume is a secondary endpoint included here due to incorporation in the GST. Ventricular volume and hippocampal volume will be measured. MRI imaging of the brain will be performed in order to measure brain atrophy over time. Imaging will be performed using cross-sectional approach for baseline and week 24 samples as well as using the longitudinal approach for baseline and week 24 pairs. Results from vMRI studies suggest that the patterns of atrophy in AD can reliably be detected and tracked across time. Hippocampal volume derived from MRI correlates with histological hippocampal volume and degree of neuronal loss and AD pathology. Longitudinal MRI measures of regional and whole brain volumetric change provide a valuable complement to cognitive measures in that they are not influenced by temporary symptomatic improvements, and they may provide an early index of the study drug's ability to reach the central nervous system and effect AD-related atrophy.

7.3 Secondary Efficacy Endpoints

7.3.1 ADAS-Cog

The ADAS-Cog is validated and widely used as a primary cognitive outcome measure in AD pharmacotherapy studies. This is a psychometric instrument that evaluates memory (immediate and delayed word recall, word recognition), attention (number cancellation), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs), and executive functioning (maze completion). Scoring is in the range of 0 to 90 with a higher score indicating greater impairment. This test will be administered by experienced raters at each site according to Table 1.

7.3.2 Dementia Severity Rating Scale (DSRS)

The DSRS is a brief 12-item questionnaire administered to an informant that assesses a subjects' functional abilities[44] and offers a global characterization of everyday activities that may be impacted by neurodegenerative disease. The DSRS is designed in a multi-choice format with strong concurrent validity and parallel content to material covered on the Clinical Dementia Rating Scale (CDR), a commonly employed dementia staging instrument[46]. The DSRS is a highly reliable scale with an intra-class correlation of >90% for interrater reliability and Cronbach's alpha > 0.70 for internal consistency[48], and has been shown to accurately discriminate between cognitive healthy individuals and dementia subjects of varying severity[44,45]. Further, the DSRS allows for a broad range of scores (total score 0-54) making it suitable to quantify a wide range of functional impairment without being hampered by floor effects seen in more advanced disease, while also making it sensitive to detecting incremental change in functional ability over time[50]. The DSRS takes about 5 minutes to administer, requires minimal rater training, and can be administered over the phone to study subjects if required. The DSRS will be administered at the Baseline, Week 12, and Week 24/Early Discontinuation Visits.

7.3.3 MoCA

Montreal Cognitive Assessment (MoCA) is commonly utilized questionnaire in clinical trials and research settings to measure levels of cognitive impairment. The MoCA measures five areas of cognitive function: orientation, visuospatial, attention and calculation, recall, and language. The MoCA will take approximately 10 minutes to complete. The test will be administered by experienced raters at each site at Screening, Week 6, Week 18, Week 24/Early Discontinuation Visit. See Appendix III (section 13.3) for the worksheet.

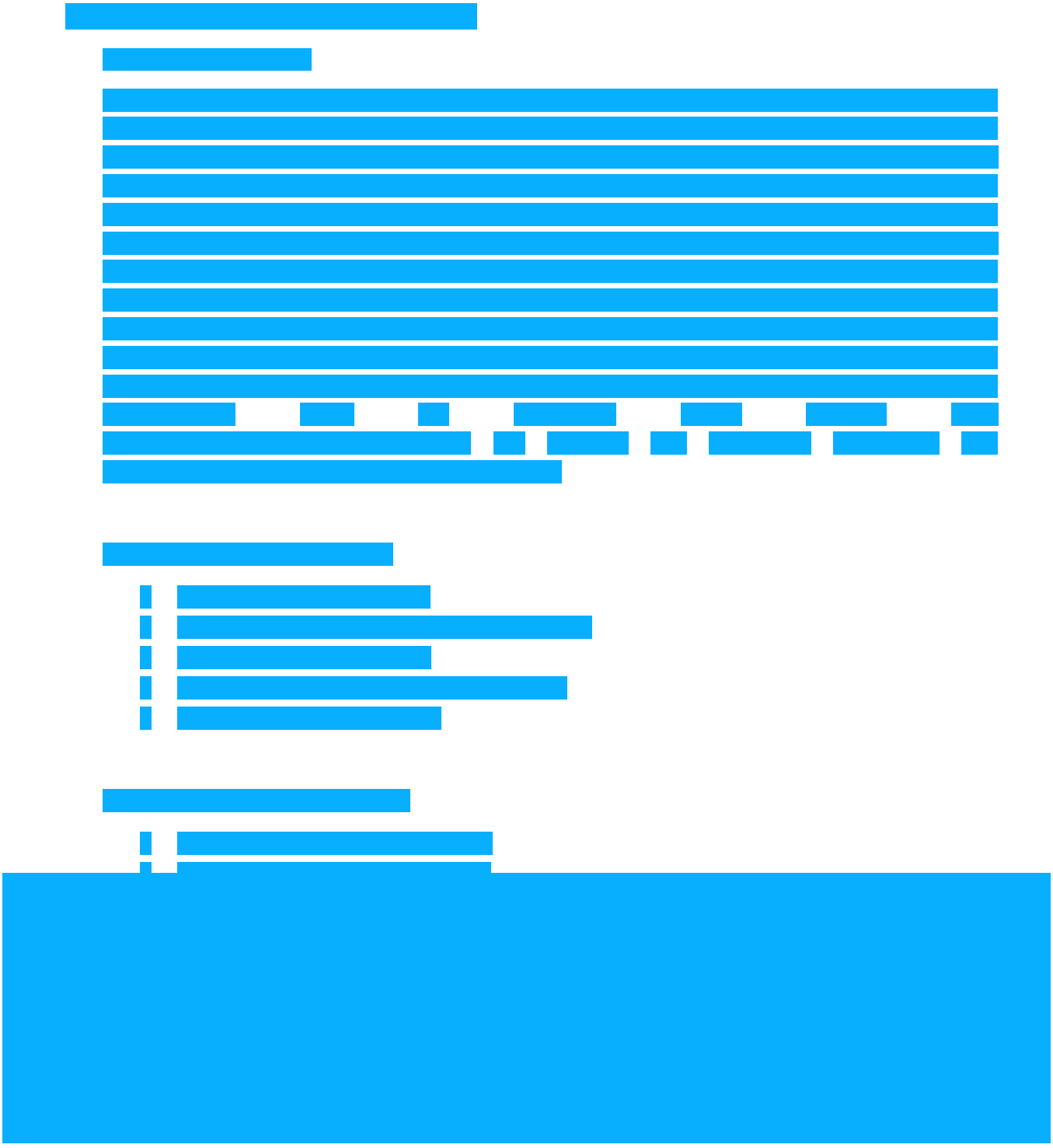
The 3 available versions of the MoCA test will be administered by experienced raters at each site. Subjects may be given any version of the MoCA at the Screening Visit as long as they have NOT received the same MoCA version clinically within the last 3 months. A different version of the MoCA should be used at each subsequent visit until Week 24 or Early Termination visit (if applicable). The MoCA version used at a study visit should be accurately documented in Source Document and within the EDC for each visit.

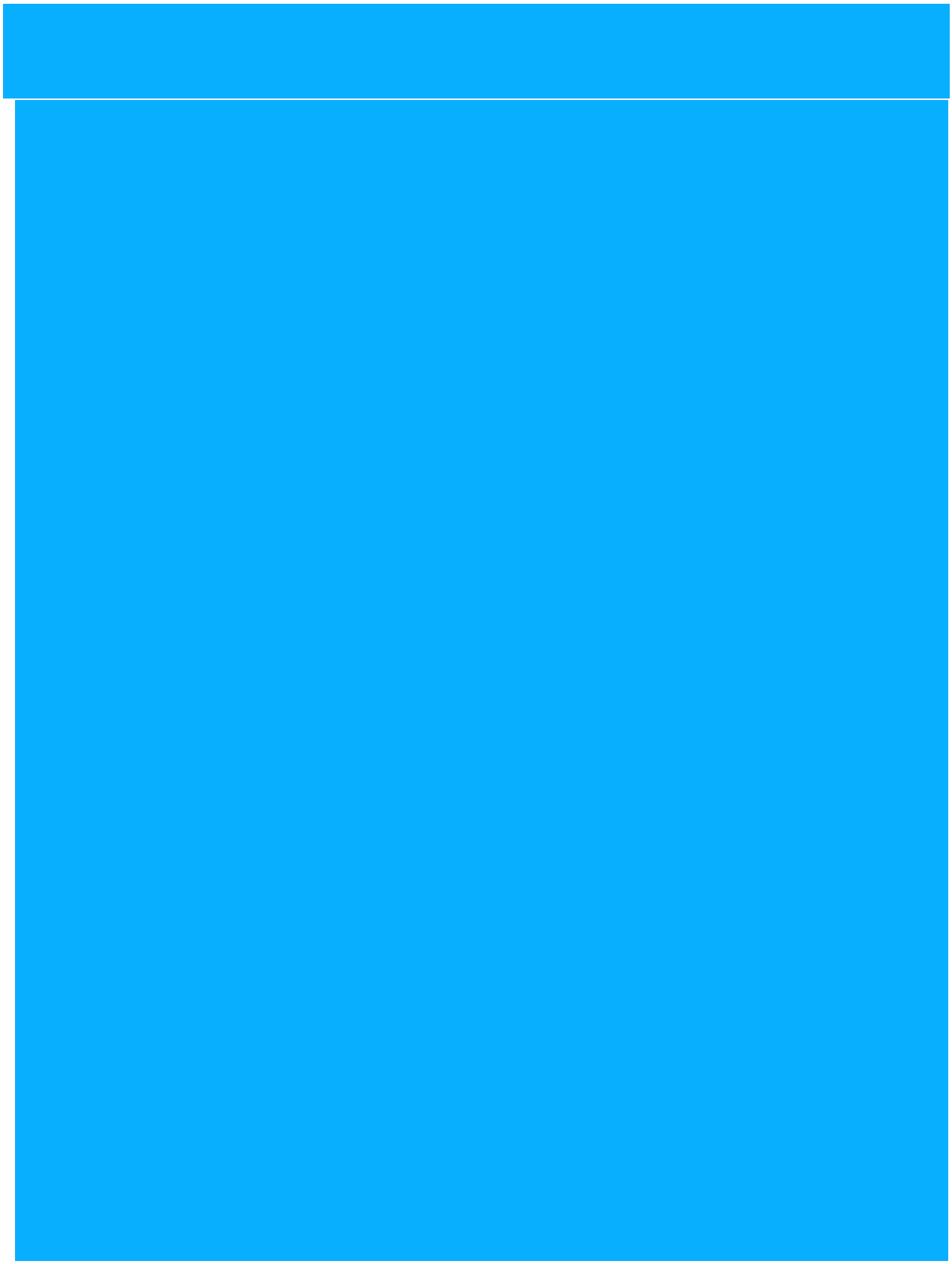
Re-screening: In cases where the subject screen fails due to the MoCA score being out of the required inclusionary range at the Screening Visit, the subject may be re-screened; a minimum of one month must have passed since their original MoCA assessment. If the subject's MoCA score was < 10, they must have had a change in therapy or intervention that (in the opinion of the SI) may have an impact on the subject's cognitive status. Subjects who move forward with a re-screen must be evaluated using a different MoCA version (7.1, 7.2 or 7.3) that was used at the original Screening Visit, and subjects may be re-screened only once.

7.3.4 NPI-Q

The Neuropsychiatric Inventory (NPI) measures dementia-related behavioral symptoms and is used to assess changes in psychological status. There are several versions of the NPI including the NPI-Questionnaire (NPI-Q), NPI-Clinician (NPI-C) and the NPI-Nursing Home (NPI-NH). All examine 12 sub-domains of behavioral functioning including:

hallucinations, delusions, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, eating abnormalities, and night-time behavioral alternations. The NPI-Q is completed by a trained rater through interview with the subject's study partner. It is well-validated and extensively used in clinical trials in AD. The NPI-Q will be administered at the Screening or Baseline, Week 12 and Week 24/Early Discontinuation Visits.





[redacted]

7.4.2.7 Additional Biomarkers

Additional biomarker panels, focused on [redacted], will likely be performed in CSF and plasma.

[redacted]

7.4.3 Pharmacokinetics

Plasma and CSF concentrations for PB, TUDCA and their respective direct metabolites will be determined on the single PK samples taken on study visit 12 and 24 (week 24 only for CSF). The plasma concentrations are intended to approximate overall exposure at steady state in patients treated with AMX0035 and provide an estimate of endogenous bile acid concentrations in patients treated with placebo. PK analyses will be detailed in a separate document.

7.5 Statistical Evaluations

Efficacy analyses will be performed in the ITT and PP populations. The Per Protocol population analysis will include individuals within the per protocol population and visit data for individuals not in this population up until the point of non-compliance (4 cumulative weeks of missed treatment or major protocol violation).

7.5.1 Primary Analyses

The GST will be a combination of 3 change-from-baseline to end-of-study endpoints (univariate components):

- Cognition (MADCOMS)
- Functional Activities Questionnaire (FAQ)
- Total Hippocampal Brain Volume (cross-sectional data)

The GST will be calculated for each subject as a mean zscore across the above 3 component endpoints for each subject in the study. This mean score will then be analyzed as the primary efficacy outcome variable.

GST individual items with right censored data will be imputed using LZCF. Intermittently missing data will be imputed using straight line imputation. Straight line imputation or z-scores will be calculated for each data collection timepoint in the study (baseline, week 6, week 12, week 18, week 24) . Let Z be the imputed z-score, while x is the last observation at timepoint t_1 and μ and σ are the mean and standard deviation of the next timepoint (t_2) for which the data is missing.

$$Z_{t2}=(x_{t1} - \mu_{t2})/\sigma_{t2}$$

Z-scores imputed relative to the group mean and standard deviation at each timepoint, will better preserve the slope of each arm and thus is more robust to differences in dropout rate across treatment. Individuals missing all post-baseline data will use the population baseline zscore to calculate LZCF by treatment group. GST will be calculated for each individual after LZCF is calculated for individual level items. LZCF imputations will be constrained by the range of the possible score for each measure.

A composite covariate will be calculated for the primary efficacy variable (GST) to adjust for baseline covariates as well as those that interact with time and will be included in the model. To calculate the composite, the change score (GST) is regressed on time. The residuals are regressed on the covariates listed below. Individual composite coefficients for each covariate are multiplied by individual covariate values and summed. A separate covariate composite is calculated for baseline covariates and baseline covariates interacting with time.

CFB will be analyzed by comparing the change between treatment group using a mixed model with repeated measures (MMRM). The MMRM will compare the estimated change from baseline between treatments for each primary endpoint. This analysis will assess whether there is a difference in estimated CFB between active and placebo groups.

The MMRM with primary outcome CFB value as the response variable will include the following covariates and fixed effects:

- Baseline composite covariate only:
  - Age (covariate);
  - baseline ADAS-Cog
  - baseline MOCA
  - baseline FAQ
  - baseline DSRS
  - baseline Hippocampal volume
  - AD/dementia status (fixed effect);
  - Concomittant use of AD medications
  - Level of Education (fixed effect split into categories of ≤12 years, >12 years);
  - Sex (fixed effect);
  - APOE4 status (fixed effect, positive or negative);

- Time composite covariate only:
  - time
  - Age*time;
  - baseline ADAS-Cog*time
  - baseline MOCA*time
  - baseline FAQ*time
  - baseline DSRS*time

- baseline Hippocampal volume*time
- AD/dementia status*time;
- Concomittant use of AD medications*time
- Level of Education*time (fixed effect split into categories of ≤12 years, >12 years);
- Sex*time;
- APOE4 status*time (positive or negative);

- Time (continuous time);
- Time by treatment interaction (Time*Treatment);
- Baseline Test Score of Efficacy Parameter (covariate);
- Site (random effect);

The covariance structure for the repeated measures in this model will be unstructured (UN). If UN does not converge for the model, the MMRM model will be simplified to allow convergence as described in the following paragraph. Variance components will be used as the covariance structure for the random site effect in the model.

Any efficacy outcomes that do not converge using the specified primary model will be rerun using a first-order heterogeneous autoregressive (ARH[1]) covariance structure, and then a compound symmetry (CS) followed by variance components (VC) structures if ARH(1) doesn't converge. The covariance structure for the site random effect will be VC.

Least-squares means will be estimated at each visit for the primary outcome. The LS mean at the endpoint is interpreted as the expected CFB in the primary outcome at the 24 week estimate drawn from the model within each group. Least squares means and standard errors will be estimated from the mixed model at all timepoints (week 12 and 24) and will be shown for all analyses. In addition, treatment differences, p-values, 95% confidence intervals for the difference, effect size, 95% confidence interval for the effect size, and an effect size based upon Cohen's D will be displayed for each comparison. Effect size will be calculated by taking the difference of LSMEANS and dividing by the standard deviation (i.e. the standard error of the estimated difference multiplied by the squared degrees of freedom). The equations below show how effect size and Cohen's D effect size will be calculated. In the following formulas *p* stands for placebo group and *t* stands for treated), *SE* for standard error and *df* for degrees of freedom:

$$Effect\ Size = \frac{LSMEAN_t - LSMEAN_p}{LSMEAN_P}$$

Cohen's d will be calculated using the following equation:

$$\text{Cohen's } d = \frac{\mu_t - \mu_p}{(pooled\ SD)},$$

where the pooled standard deviation (pooled SD) is defined as follows:

$$Pooled\ SD = \sqrt{\frac{((n_t - 1)(SE_t\sqrt{n_t})^2 + ((n_p - 1)(SE_p\sqrt{n_p})^2}{(n_t + n_p - 1)}}.$$

The number of subjects with an observed efficacy outcome, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum will all be reported and accompany the estimates from the MMRM outlined in this section (Tables 14.2.1-14.2.16).

7.5.1.1 Covariate and Categorical Interaction Analyses

The following variables will be assessed for interactions with the primary efficacy variable and time using the MMRM as described above:

- baseline score (for outcome being analyzed)
- baseline MoCA score
- ApoE4(carrier/non-carrier; discrete)
- ApoE4(number of E4 alleles; discrete)

Estimates for continuous variables will be drawn at the first and third quartiles.

An MMRM without imputation will be performed as a sensitivity analysis. The same MMRM parameters described above will be used. Additionally, an MMRM will be run for the primary analysis using MRI quantitative data generated with the longitudinal approach.

7.5.2 Secondary Analyses

All secondary endpoints CFB values will be analyzed using the MMRM described above. This analysis will assess whether or not there is a difference in estimated CFB values between treatment groups and placebo at the 24 week model estimate using least squares means estimates from the MMRM model.

7.5.2.1 PK Analyses

PK will be analyzed using the ITT population. Descriptive statistics will be provided for the AMX0035 and placebo treatment groups. Additionally, correlations of exposure values to clinical outcomes may be assessed, if possible, by correlation to concentration data as well as summarization of outcomes data in the upper and lower PK tertiles.

The PK concentration data collected prior to each dose may be used in a concentration response relationship analysis to assess correlation with each outcome which will mirror the primary analysis but replace the treatment variable with PK concentration. Analysis may be performed separately for each PK collection time as well as using the higher of both PK timepoints.

[redacted]

8 Safety

8.1 Safety Endpoints

Primary endpoint

- incidence of treatment emergent Grade II-IV adverse events (includes moderate/ severe/ serious adverse events)

Additional endpoints

- Incidence and severity of treatment emergent adverse events (AEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- ECGs
- Use of concomitant medications for treatment of AEs
- C-SSRS

8.2 Analysis Populations Evaluated for Safety

All analyses of safety will be performed on the Safety Population.

8.3 Statistical Methods for Safety Endpoints

A summary table will be provided for the Safety Population of the count and percentage of subjects with any safety endpoint. No hypothesis testing will be performed for safety variables.

8.4 Adverse Events

AEs reported on CRFs will be coded into system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA v23.1). A treatment-emergent adverse event (TEAE) is defined as an AE with an onset date on or after the start of dosing. The adverse event summary will include only TEAEs. Any AEs that are not considered treatment-emergent will be provided in data listings only.

The incidence of AEs will be summarized for the safety population. Although a preferred term or system organ class may be reported more than once for a subject, each subject will only be counted once in the incidence count for each category. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (definite > probable > possible > unlikely > not related) recorded for the event will be presented.

Severity levels include: mild, moderate and severe. Relationships will be grouped into two categories for analysis: related and unrelated. Not related and unlikely will be categorized as "unrelated." Possible, probable and definite will be categorized as "related." If severity or drug relationship is missing no data imputation will be performed and no category of missing will be presented.

Summary tables showing the number of subjects and percent within each category will be generated for each of the following types of adverse events:

- All AEs;
- Fatal Adverse Events;
- AEs for Subjects who Died.
- AEs with concomitant medications

These summaries will present the number and percentage of subjects reporting an adverse event for each classification level. The denominators for calculating the percentages overall will be based on the number of subjects in the safety population. The denominators for calculating the percentages by treatment will be based on the number of subjects exposed to each treatment in the safety population. In addition to these summaries, all AEs will be summarized by action taken, seriousness, severity, and relationship to study drug.

All AEs that occurred in 5% or more of all subjects (active and placebo) will be tabulated for the safety population. These results will be analyzed descriptively and their incidence rate and two-sided 95% confidence intervals will be summarized. In addition, the risk ratio and its 95% confidence intervals between active and placebo will be calculated in order to estimate the occurrence of side effects and adverse events.

All SAEs, AEs leading to premature discontinuation from the study, AEs with fatal outcome, and AEs for subjects who died will also be provided in data listings by subject and preferred term.

8.5 Vital Signs

Each vital sign will be summarized by treatment and overall by visit, using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects) for the safety population. Additionally, descriptive summaries will be provided for CFB values for each treatment by visit for vital sign measurements collected during the study.

The latest non-missing vital sign value collected prior to dosing will be used as the baseline values. The baseline values will usually be the vital signs recorded at the baseline visit. In the case of repeated vital signs, the last collected values within that visit will be used for the summary tables.

Vital signs will be provided in a data listing by subject, visit, and parameter.

8.6 Electrocardiogram

ECG values and change from baseline values will be summarized by visit using descriptive statistics. ECG abnormalities will be summarized as the count and percentage of subjects in each treatment group. CFB will be summarized in a shift table crossing baseline and each visit result. The denominators for calculating the percentages will be the number of subjects in each treatment group who have an evaluation for both the screening and each visit in the safety population. These results will be analyzed descriptively and their incidence rate and two-sided 95% confidence intervals will be summarized.

8.7 Clinical Laboratory Evaluations

Continuous blood clinical laboratory analytes absolute values and change from baseline values will be summarized by analyte and visit using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects). Mean line plots over time will be displayed for each analyte with separate lines for each treatment. Categorical laboratory analytes, classified as normal or abnormal, will be summarized by analyte and visit using the number and percentage of subjects in each category. The denominators for calculating the percentages will be based on the number of subjects with non-missing assessments at a particular visit for the safety population. The latest non-missing clinical laboratory tests collected prior to dosing will be used as the baseline values.

Shifts to values outside of the normal range will be presented by analyte and will be summarized by the number and percentage of subjects with shifts. Shifts will be determined for analytes in which both the baseline value and the termination value are recorded. The denominators for calculating the percentages will be based on the number of subjects with non-missing assessments for a particular analyte.

Clinical laboratory results will be provided in data listings by subject, visit and analyte. Abnormal lab results will be provided in a separate listing by subject, center, analyte and visit.

8.8 Physical and Neurological Exams

Physical and neurological examination findings will be summarized as the count and percentage of subjects in each treatment group.

8.9 C-SSRS

The C-SSRS responses will be tabulated by visit, treatment group, question and response. All C-SSRS responses will also be provided in a data listing.

9 Other Listings

The following additional listings will be provided:

- Subjects excluded from the safety, mITT, and PP populations;
- Clinical laboratory results for hematology, blood chemistry and urinalysis;
- Abnormal laboratory results;
- Physical examination assessments;
- Neurological examination assessments;
- Concomitant medications;
- Dose administration dates and times.

Other Listings

10 Bibliography

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