Protocol Title:

A Phase 2, Prospective, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease

Protocol Number:

XAN-TTS-AD-001

Amendment Number:

Version 1.0

Amendment Scope:

Global

Country/Region Identifier:

Global

Compound:

Xanomeline

Brief Title:

A study to investigate cognitive function and global clinical status with xanomeline transdermal therapeutic system compared with placebo in participants aged 50 to 85 years of age with mild to moderate Alzheimer's disease

Study Phase:

Phase 2

Acronym:

XAN-TTS-AD

Sponsor Name:

Maxis

Legal Registered Address:

[To be provided by Sponsor]

Manufacturer:

Maxis Pharmaceuticals

Regulatory Agency Identifier Number(s):

[To be provided by Sponsor]

Sponsor Signatory:

Name: [To be provided by Sponsor]

Title: [To be provided by Sponsor]

Date: [To be provided by Sponsor]

Medical Monitor Name and Contact Information:

[To be provided by Sponsor]

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY

Document	Date
Original Protocol	Day-Mon-Year

This amendment is considered to be substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament because it significantly impacts the safety or physical/mental integrity of participants and the scientific value of the study.

Overall Rationale for the Amendment:

Not applicable for original protocol.

Table of Contents

List of Abbreviations and Definitions of terms

reviation	Definition/Explanation
	Alzheimer's Disease
S-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
	Adverse Event
OVA	Analysis of Covariance
C+	Clinician's Interview-Based Impression of Change Plus Caregiver Input
	Central Nervous System
	Electrocardiogram
	Informed Consent Form
	International Council for Harmonisation
EC	Institutional Review Board/Independent Ethics Committee
RM	Mixed Model Repeated Measures
SE	Mini-Mental State Examination
X	Neuropsychiatric Inventory-X
CDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associ
	Serious Adverse Event
	Transdermal Therapeutic System

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 2, Prospective, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease

Brief Title:

A study to investigate cognitive function and global clinical status with xanomeline transdermal therapeutic system compared with placebo in participants aged 50 to 85 years of age with mild to moderate Alzheimer's disease

Regulatory Agency Identifier Number(s):

[To be provided by Sponsor]

Pediatric Investigational Plan Number:

Not applicable

Rationale:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, behavioral disturbances, and impairment in activities of daily living. Current approved treatments provide modest symptomatic benefits but do not alter the underlying disease progression. Xanomeline is a selective muscarinic M1/M4 receptor agonist that has shown potential cognitive benefits in previous studies. The transdermal therapeutic system (TTS) delivery method is being investigated to improve tolerability while maintaining efficacy compared to oral administration.

Objectives, Endpoints, and Estimands:

	Endpoints
S (50 cm², 75 cm², and 100 cm²) compared with placebo on cognitive function in patients with mild to moderate AD	Change from baseline in ADA
S (50 cm², 75 cm², and 100 cm²) compared with placebo on global clinical status in patients with mild to moderate AD	CIBIC+ score at Week 24
nomeline TTS on cognition	Change from baseline in ADA
nomeline TTS on global clinical status	CIBIC+ score at Weeks 8 and
on behavioral symptoms	Mean change from baseline i

Overall Design Synopsis:

This study design includes double-blind masking.

Brief Summary:

The purpose of this study is to measure cognitive function and global clinical status with xanomeline transdermal therapeutic system compared with placebo in participants with mild to moderate Alzheimer's disease.

Study details include:

- The study duration will be up to 26 weeks.
- The treatment duration will be 24 weeks.
- The visit frequency will be approximately every 4 weeks.

Number of Participants:

Approximately 400 participants will be randomized in a 1:1:1:1 ratio to receive placebo, xanomeline TTS 50 cm², xanomeline TTS 75 cm², or xanomeline TTS 100 cm² (100 participants per treatment arm).

Study Arms and Duration:

- Placebo TTS: Two patches applied daily for 24 weeks
- Xanomeline TTS 50 cm²: Two patches (50 cm² each) applied daily for 24 weeks
- Xanomeline TTS 75 cm²: Two patches (75 cm² each) applied daily for 24 weeks
- Xanomeline TTS 100 cm²: Two patches (100 cm² each) applied daily for 24 weeks

Data Monitoring/Other Committee: Yes

A data monitoring committee has been appointed for this study. The data monitoring committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

1.2. Schema

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Screening Period (≤14 days) → Randomization (1:1:1:1) → Treatment Arms: - Placebo TTS (n=100): Two patches applied daily for 24 weeks - Xanomeline TTS 50 cm² (n=100): Two patches applied daily for 24 weeks - Xanomeline TTS 75 cm² (n=100): Two patches applied daily for 24 weeks - Xanomeline TTS 100 cm² (n=100): Two patches applied daily for 24 weeks Treatment Period: 24 weeks with assessments at Weeks 4, 8, 12, 16, 20, and 24 Follow-up Period: 2 weeks after last dose
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1.3. Schedule of Activities (SoA)

before Day 1)	Baseline (Day 1)	Treatment Period	E/D	Fo
	Week 12	Week 16	Week 20	W
	X	Recheck clinical status before randomization and/or first dose of investigational intervention		
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	X
	X	X	X	X

E/D = Early Discontinuation

2. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, behavioral disturbances, and impairment in activities of daily living. It is the most common cause of dementia, affecting an estimated 50 million people worldwide, with numbers projected to increase dramatically as the population ages. Current approved treatments provide modest symptomatic benefits but do not alter the underlying disease progression.

Xanomeline is a novel, potent, and selective muscarinic M1/M4 receptor agonist that has shown potential cognitive benefits in previous studies of AD. The cholinergic system plays a critical role in memory and cognition, and cholinergic deficits are a hallmark of AD pathology. By selectively targeting M1/M4 receptors, xanomeline aims to enhance cholinergic neurotransmission while minimizing peripheral cholinergic side effects associated with non-selective muscarinic agonists.

2.1. Study Rationale

Previous clinical studies with oral xanomeline demonstrated promising efficacy in improving cognitive function and behavioral symptoms in patients with AD. However, the oral formulation was associated with significant peripheral cholinergic side effects, including gastrointestinal disturbances, excessive sweating, and hypersalivation, which limited its clinical utility.

The transdermal therapeutic system (TTS) has been developed to deliver xanomeline through the skin, potentially providing more stable plasma concentrations while reducing peak plasma levels associated with adverse events. This approach aims to maintain the cognitive benefits of xanomeline while improving tolerability compared to oral administration.

This Phase 2 study is designed to evaluate the efficacy and safety of three dose levels of xanomeline TTS compared to placebo in patients with mild to moderate AD. The results will inform the design of future Phase 3 studies and help determine the optimal dose for further development.

2.2. Background

Cholinergic deficits are a well-established feature of AD pathology, with significant loss of cholinergic neurons in the basal forebrain and reduced acetylcholine levels in the cortex and hippocampus. This cholinergic dysfunction correlates with cognitive impairment and has been a primary target for symptomatic treatment of AD.

Currently approved treatments for AD include acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the NMDA receptor antagonist memantine. While these medications provide modest symptomatic benefits, there remains a significant unmet need for more effective treatments that can meaningfully impact disease progression and improve quality of life for patients and caregivers.

Xanomeline is a selective muscarinic M1/M4 receptor agonist that directly stimulates postsynaptic muscarinic receptors, potentially offering advantages over acetylcholinesterase inhibitors, which indirectly increase acetylcholine levels. In a previous 6-month, randomized, double-blind, placebo-controlled trial in patients with mild to moderate AD, oral xanomeline demonstrated dose-dependent improvements in cognitive function, global clinical status, and behavioral symptoms. However, peripheral cholinergic side effects led to high discontinuation rates, particularly at higher doses.

The xanomeline TTS has been developed to improve the tolerability profile while maintaining efficacy. Preclinical studies and Phase 1 trials have demonstrated that transdermal delivery of xanomeline results in more stable plasma concentrations and reduced peak plasma levels compared to oral administration, potentially reducing the incidence and severity of cholinergic side effects.

A detailed description of the chemistry, pharmacology, efficacy, and safety of xanomeline is provided in the investigator's brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of xanomeline TTS may be found in the investigator's brochure, participant information leaflet, and development safety update report (DSUR).

2.3.1. Risk Assessment

The potential risks associated with xanomeline TTS include:

1. **Cholinergic side effects**: While the transdermal formulation is expected to reduce the incidence and severity of peripheral cholinergic side effects compared to oral administration, patients may still experience nausea, vomiting, diarrhea, excessive sweating, hypersalivation, and urinary urgency. These effects are expected to be dose-dependent and generally mild to moderate in severity.

2. **Cardiovascular effects**: Muscarinic receptor agonists may affect heart rate and blood pressure. ECG monitoring and vital sign assessments will be performed throughout the study to monitor for potential cardiovascular effects.

3. **CNS effects**: Cholinergic stimulation may potentially cause dizziness, headache, and sleep disturbances. Patients will be monitored for these effects throughout the study.

4. **Skin reactions**: The transdermal delivery system may cause local skin reactions at the application site, including erythema, pruritus, and irritation. Patch application sites will be rotated, and skin reactions will be monitored throughout the study.

Risk mitigation strategies include:

- Careful patient selection based on inclusion/exclusion criteria
- Regular monitoring of adverse events, vital signs, and ECG
- Dose modification or discontinuation guidelines for managing adverse events
- Rotation of patch application sites to minimize skin reactions

• Provision of clear instructions to patients and caregivers regarding patch application and potential side effects

2.3.2. Benefit Assessment

The potential benefits of xanomeline TTS include:

1. **Improved cognitive function**: Based on previous studies with oral xanomeline, the TTS formulation may improve cognitive function in patients with mild to moderate AD.

2. **Improved global clinical status**: Xanomeline may improve overall clinical status and functioning in daily activities.

3. **Reduced behavioral symptoms**: Previous studies with oral xanomeline showed improvements in behavioral symptoms associated with AD, which may also be observed with the TTS formulation.

4. **Improved tolerability**: The TTS formulation is expected to provide a more favorable tolerability profile compared to oral xanomeline, potentially allowing more patients to benefit from treatment.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with xanomeline TTS are justified by the anticipated benefits that may be afforded to patients with mild to moderate Alzheimer's disease. The unmet medical need in this population is significant, and xanomeline TTS has the potential to provide meaningful clinical benefits with an improved tolerability profile compared to oral xanomeline.

3. Objectives, Endpoints, and Estimands

	Endpoints
compared with placebo on cognitive function in patients with mild to moderate AD	Change from baseline in ADAS-Cog (11) total score at Week 2
compared with placebo on global clinical status in patients with mild to moderate AD	CIBIC+ score at Week 24
	Change from baseline in ADAS-Cog (11) total score at Weeks
tatus	CIBIC+ score at Weeks 8 and 16

	Mean change from baseline in NPI-X score from Week 4 to We
	Incidence of treatment-emergent adverse events (TEAEs), ser
ory values	

Estimand(s) for Primary Objective(s)

Primary estimand for ADAS-Cog (11)

The primary clinical question of interest is:

What is the population-level summary in change from baseline to Week 24 in ADAS-Cog (11) total score in patients with mild to moderate Alzheimer's disease treated with xanomeline TTS vs. placebo regardless of discontinuation of investigational intervention for any reason and regardless of initiation of rescue medication or change in background medication (dose and product)?

The estimand is described by the following attributes:

- **Population**: Patients with mild to moderate Alzheimer's disease (MMSE 10-23)
- **Endpoint**: Change from baseline to Week 24 in ADAS-Cog (11) total score
- **Treatment condition**: The investigational interventions regardless of discontinuation for any reason, with or without rescue medication or change in background medication (treatment policy strategy)
- **Remaining intercurrent events**: The intercurrent events "intervention discontinuation for any reason" and "initiation of rescue medication or change in background medication (dose and product)" are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.
- **Population-level summary**: Difference in mean changes between treatment conditions

Rationale for estimand: This estimand reflects the effect of treatment as would be expected in clinical practice where patients may discontinue treatment or require additional medications.

Primary estimand for CIBIC+

The primary clinical question of interest is:

What is the population-level summary in CIBIC+ score at Week 24 in patients with mild to moderate Alzheimer's disease treated with xanomeline TTS vs. placebo regardless of discontinuation of investigational intervention for any reason and regardless of initiation of rescue medication or change in background medication (dose and product)?

The estimand is described by the following attributes:

- **Population**: Patients with mild to moderate Alzheimer's disease (MMSE 10-23)
- **Endpoint**: CIBIC+ score at Week 24
- **Treatment condition**: The investigational interventions regardless of discontinuation for any reason, with or without rescue medication or change in background medication (treatment policy strategy)
- **Remaining intercurrent events**: The intercurrent events "intervention discontinuation for any reason" and "initiation of rescue medication or change in background medication (dose and product)" are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.
- **Population-level summary**: Difference in mean scores between treatment conditions

Rationale for estimand: This estimand reflects the effect of treatment as would be expected in clinical practice where patients may discontinue treatment or require additional medications.

Estimands for Secondary Objectives

Secondary estimands for the time course of effects on cognition and global clinical status will follow the same structure as the primary estimands but will focus on the Week 8 and Week 16 timepoints.

Secondary estimand for behavioral symptoms:

The clinical question of interest is:

What is the difference in the mean change from baseline in NPI-X score from Week 4 to Week 24 in patients with mild to moderate Alzheimer's disease treated with xanomeline TTS vs. placebo regardless of discontinuation of investigational intervention for any reason and regardless of initiation of rescue medication or change in background medication?

The estimand is described by the following attributes:

- **Population**: Patients with mild to moderate Alzheimer's disease (MMSE 10-23)
- **Endpoint**: Mean change from baseline in NPI-X score from Week 4 to Week 24
- **Treatment condition**: The investigational interventions regardless of discontinuation for any reason, with or without rescue medication or change in background medication (treatment policy strategy)
- **Remaining intercurrent events**: The intercurrent events "discontinuation of investigational intervention for any reason" and "initiation of rescue medication or change in background medication" are addressed by the treatment condition attribute using the treatment policy strategy. There are no remaining intercurrent events anticipated at this time.
- **Population-level summary**: Difference in mean changes between treatment conditions

Rationale for estimand: This estimand reflects the effect of treatment on behavioral symptoms as would be expected in clinical practice.

4. Study Design

4.1. Overall Design

This is a Phase 2, prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of the xanomeline transdermal therapeutic system (TTS) in patients with mild to moderate Alzheimer's disease.

Approximately 400 patients will be randomized in a 1:1:1:1 ratio to receive one of the following treatments for 24 weeks:

- Placebo TTS
- Xanomeline TTS 50 cm²
- Xanomeline TTS 75 cm²
- Xanomeline TTS 100 cm²

The study will consist of a screening period of up to 14 days, a 24-week treatment period, and a 2-week follow-up period. During the treatment period, patients will apply two patches daily to the upper back, upper arm, or chest, with patch application sites rotated to minimize skin reactions.

Efficacy assessments will include the ADAS-Cog (11), CIBIC+, and NPI-X. Safety assessments will include adverse event monitoring, vital signs, ECG, clinical laboratory tests, and patch application site assessments.

4.2. Scientific Rationale for Study Design

The randomized, double-blind, placebo-controlled, parallel-group design is the gold standard for evaluating the efficacy and safety of investigational treatments. This design minimizes bias and allows for a robust assessment of the treatment effect compared to placebo.

The 24-week treatment duration is consistent with previous AD clinical trials and is considered sufficient to detect clinically meaningful changes in cognitive function and global clinical status. The inclusion of three dose levels (50 cm², 75 cm², and 100 cm²) will help establish the dose-response relationship and identify the optimal dose for future Phase 3 studies.

The primary efficacy endpoints, ADAS-Cog (11) and CIBIC+, are well-established and widely accepted measures for assessing cognitive function and global clinical status in AD clinical trials. The ADAS-Cog (11) is a comprehensive cognitive assessment tool that evaluates multiple cognitive

domains affected in AD, while the CIBIC+ provides a clinician's global assessment of change in a patient's clinical status, incorporating caregiver input.

The inclusion of the NPI-X as a secondary endpoint allows for the assessment of behavioral symptoms, which are common in AD and significantly impact patient and caregiver quality of life.

4.2.1. Patient Input into Design

4.2.1.1 Obtaining Study Participant Feedback (Voluntary):

This trial will include an option for patients to complete a questionnaire, the 'Study Participant Feedback Questionnaire', which will give participants the opportunity to provide feedback on their clinical trial experience. Participants may be asked to complete a survey, at one or more timepoints, to collect feedback on their experience with participation in the clinical trial. Individual participant level responses will be anonymous to the investigator and site staff and so will not be reviewed by investigators. Coded responses would be used by the sponsor to understand where improvements can be made in the clinical trial process. We may combine responses across studies and with data collected as part of the study, such as demographics, to investigate correlations with the participant experience. We may share aggregated data, maintaining individuals' anonymity, with site staff so they can take steps to understand and improve the participant experience at their site. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or adverse events and therefore would not be trial data. Consequently, this data does not contribute to any endpoints on the study and will be analyzed and reported separately from the clinical study data. The results of this participant experience analysis may be published or presented at scientific meetings, with the Sponsor complying with the requirements for publication. Should any spontaneous information be collected about AEs, this would be reported and transferred to the safety database.

4.3. Justification for Dose

The selection of the 50 cm^2, 75 cm^2, and 100 cm^2 doses for this study is based on pharmacokinetic data from Phase 1 studies and the efficacy and safety profile observed with oral xanomeline in previous clinical trials.

Phase 1 studies demonstrated that the 50 cm^2, 75 cm^2, and 100 cm^2 TTS formulations provide steady-state plasma concentrations comparable to oral doses that showed efficacy in previous AD trials, but with reduced peak plasma levels, potentially improving tolerability. The three dose levels included in this study will help establish the dose-response relationship and identify the optimal dose for future development.

The addition of the 100 cm^2 dose level aims to explore whether higher doses can provide additional efficacy benefits while maintaining an acceptable safety profile with the transdermal delivery system.

4.4. End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study globally.

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 50 to 85 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.

3. Mini-Mental State Examination (MMSE) score of 10 to 23, inclusive, at screening.

4. Evidence of cognitive decline over at least 6 months prior to screening, as documented by medical history.

5. Brain imaging (CT or MRI) within 12 months prior to screening (or during screening) consistent with a diagnosis of AD and excluding other causes of dementia.

6. Availability of a reliable caregiver who has regular contact with the participant (at least 10 hours per week), can accompany the participant to study visits, and can provide accurate information about the participant's functioning.

Weight

7. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5 – 35.0 kg/m² (inclusive).

Sex and Contraceptive/Barrier Requirements

8. Male and female participants, inclusive of all gender identities.

Contraceptive use by participants or participant partners should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants:

Male participants must agree to use contraception during the treatment period and for at least 30 days after the last dose of study intervention and refrain from donating sperm during this period if sexually active with a female of childbearing potential.

Female participants:

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)
- Is a WOCBP and using a highly effective method of contraception during the treatment period and for at least 30 days after the last dose of study intervention

Informed Consent

9. Signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Both the participant and caregiver must provide written informed consent.

Other Inclusion Criteria

10. Able to comply with the study protocol procedures, including the application of transdermal patches.

5.2. Exclusion Criteria

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

Medical Conditions

1. Dementia due to causes other than Alzheimer's disease, including but not limited to vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease with dementia, or normal pressure hydrocephalus.

2. History of seizures within 2 years prior to screening or history of more than one seizure episode after the age of 18 years.

3. History of stroke within 1 year prior to screening or evidence of clinically significant cerebrovascular disease.

4. Clinically significant cardiovascular disease, including:

- Myocardial infarction within 1 year prior to screening
- Unstable angina
- Congestive heart failure (New York Heart Association Class III or IV)
- Clinically significant cardiac arrhythmia requiring treatment
- Uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg)

5. History of gastrointestinal disease or surgery that could affect drug absorption.

6. Clinically significant psychiatric illness, including major depression, bipolar disorder, schizophrenia, or other psychotic disorder, that is not well-controlled or that required hospitalization within 6 months prior to screening.

7. Current clinically significant skin conditions that would interfere with patch application or assessment of skin reactions, including but not limited to psoriasis, eczema, or atopic dermatitis affecting potential patch application sites.

8. Known hypersensitivity to xanomeline or any components of the transdermal patch.

Liver Safety

9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN); alkaline phosphatase or total bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).

10. Clinically significant hepatic impairment (Child-Pugh Class B or C).

Prior/Concomitant Therapy

11. Use of investigational drugs within 30 days or 5 half-lives (whichever is longer) prior to screening.

12. Current use of strong inhibitors or inducers of cytochrome P450 3A4.

13. Initiation of or change in dose of cholinesterase inhibitors or memantine within 3 months prior to screening. Participants on stable doses of these medications for at least 3 months prior to screening may be included.

14. Current use of medications with significant anticholinergic activity, including tricyclic antidepressants, first-generation antihistamines, and certain antipsychotics.

Prior/Concurrent Clinical Study Experience

15. Participation in another clinical study with an investigational product within 30 days prior to screening.

Diagnostic Assessments

16. Clinically significant abnormalities in laboratory tests, ECG, or physical examination at screening that, in the investigator's opinion, would preclude participation in the study.

17. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) formula.

Other Exclusion Criteria

18. History of alcohol or substance abuse within 1 year prior to screening.

19. Any condition that, in the opinion of the investigator, would preclude participation in the study or prevent compliance with study procedures.

5.3. Lifestyle Considerations

- Participants should maintain their usual diet and level of physical activity throughout the study.
- Participants and caregivers should be instructed on proper patch application and rotation of application sites.

5.3.1. Meals and Dietary Restrictions

No specific dietary restrictions are required for this study.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants should maintain their usual caffeine intake throughout the study.
- Excessive alcohol consumption (more than 2 standard drinks per day) should be avoided.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted at patch application sites.

5.3.3. Activity

Participants should maintain their usual level of physical activity throughout the study.

5.3.4. Other Restrictions

Participants should avoid applying lotions, creams, or oils to the patch application sites.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Enrollment, randomization, or administration of study intervention may be temporarily delayed for the following reasons:

- Acute illness or infection

• Abnormal laboratory values or vital signs that, in the investigator's opinion, require further evaluation or treatment before study participation

• Skin conditions that would interfere with patch application but are expected to resolve within the screening period

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

Table 1. Study Intervention(s) Administered

m²	Xanomeline TTS 100 cm²
ning xanomeline, 75 cm² size, applied twice daily	Transdermal patch containing xanomeline, 100 cm² si
	Drug
	Transdermal patch
pproximately X mg/day of xanomeline	100 cm² patch delivering approximately X mg/day of x
ed daily	Two 100 cm² patches applied daily
	Transdermal
	Experimental
	IMP
sponsor	Provided centrally by the sponsor
provided in sealed pouches. Each pouch will be labeled as required per country requirement.	Study intervention will be provided in sealed pouches.
	Xanomeline

Table 2. Study Arm(s)

omeline TTS 50 cm²	Xanomeline TTS 75 cm²
imental	Experimental
ipants will receive xanomeline TTS 50 cm² patches applied twice daily for 24 weeks.	Participants will receive xanomeline TTS 75 cm² patches applie

meline TTS 50 cm²	Xanomeline TTS 75 cm²

6.1.1. Rescue Medicine

No specific rescue medications are planned for this study. Management of adverse events will be according to standard medical practice at the discretion of the investigator.

6.1.2. Medical Devices

1. The sponsor manufactured medical devices provided for use in this study are the transdermal therapeutic system (TTS) patches containing xanomeline or placebo.

2. Instructions for medical device use are provided in the patient information leaflet and will be reviewed with participants and caregivers at the baseline visit.

3. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants randomized/assigned to study intervention may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.

3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

4. The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

5. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual or other specified location.

6.3. Assignment to Study Intervention

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

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

Returned study intervention should not be redispensed to the participants.

6.4. Blinding, Masking

This is a double-blind study in which participants/care providers/investigators/outcomes assessors are blinded to study intervention. The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

6.5. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned patches, etc. during the study visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

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

6.6. Dose Modification

If a participant experiences intolerable adverse events related to the study intervention, the investigator may temporarily discontinue the study intervention for up to 7 days. If the adverse events resolve or improve to a tolerable level within this period, the study intervention may be resumed. If the adverse events persist beyond 7 days or recur upon rechallenge, the participant should be discontinued from the study intervention but encouraged to remain in the study for follow-up assessments.

6.6.1. Retreatment Criteria

Not applicable for this study.

6.7. Continued Access to Study Intervention after the End of the Study

Participants will not have continued access to the study intervention after the end of the study. Participants who complete the study or who discontinue study intervention early will be managed according to standard medical practice.

6.8. Treatment of Overdose

For this study, any application of more than the prescribed number of patches within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9. Prior and Concomitant Therapy

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

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

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

The following medications are permitted during the study:

- Stable doses of cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and/or memantine if started at least 3 months prior to screening and maintained at a stable dose throughout the study
- Acetaminophen/Paracetamol, at doses of ≤ 2 grams/day
- Antidepressants (except those with significant anticholinergic activity) if started at least 1 month prior to screening and maintained at a stable dose throughout the study
- Antihypertensives, if started at least 1 month prior to screening and maintained at a stable dose throughout the study

The following medications are prohibited during the study:

- Strong inhibitors or inducers of cytochrome P450 3A4
- Medications with significant anticholinergic activity, including tricyclic antidepressants, first-generation antihistamines, and certain antipsychotics
- Other investigational drugs

Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

7.1. Discontinuation of Study Intervention

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

Participants must discontinue study intervention for any of the following reasons:

- Participant or caregiver request
- Pregnancy
- Significant protocol deviation
- Non-compliance with study intervention or protocol procedures
- Adverse event that, in the opinion of the investigator or sponsor, contraindicates further dosing
- Lost to follow-up
- Study terminated by sponsor
- Death

7.1.1. Liver Event Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Participants with ALT or AST > 3 × ULN and total bilirubin > 2 × ULN (> 35% direct bilirubin) or ALT or AST > 3 × ULN and INR > 1.5 (if INR measured) must discontinue study intervention immediately.

7.1.2. QTc Stopping Criteria

Participants with QTc > 500 msec or QTc increase from baseline > 60 msec must discontinue study intervention.

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

7.1.3. Temporary Discontinuation

Temporary discontinuation of study intervention for up to 7 days is permitted for participants who develop adverse events that, in the opinion of the investigator, warrant temporary withdrawal of study intervention but are expected to resolve within this timeframe. If the adverse events resolve or improve to a tolerable level within 7 days, the study intervention may be resumed. If the adverse events persist beyond 7 days or recur upon rechallenge, the participant should be permanently discontinued from the study intervention but encouraged to remain in the study for follow-up assessments.

7.1.4. Rechallenge

7.1.4.1. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are not allowed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason) without any negative consequences.
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

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

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 200 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and General/Baseline Procedures

The following procedures will be performed at screening and/or baseline as indicated in the SoA:

- Informed consent
- Demographic information
- Medical history
- Prior and concomitant medication review
- Inclusion/exclusion criteria review
- Assignment of participant number
- Randomization

8.2. Efficacy and/or Immunogenicity Assessments

The following efficacy assessments will be performed at the timepoints specified in the SoA:

ADAS-Cog (11)

The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) is a widely used instrument designed to assess cognitive function in patients with Alzheimer's disease. The 11-item version includes assessments of memory, language, praxis, and orientation. Scores range from 0 to 70, with higher scores indicating greater cognitive impairment. The ADAS-Cog will be administered by trained raters who have demonstrated reliability and consistency in administration and scoring.

CIBIC+

The Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+) is a global assessment of change in clinical status from baseline. It incorporates information from both the patient and caregiver and evaluates four domains: general, cognitive, behavior, and activities of daily living. The CIBIC+ is scored on a 7-point scale, where 1 indicates marked improvement, 4 indicates no change, and 7 indicates marked worsening. The CIBIC+ will be administered by clinicians who are blinded to other efficacy assessments and adverse events.

NPI-X

The Neuropsychiatric Inventory-X (NPI-X) assesses behavioral symptoms commonly observed in patients with dementia, including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating changes. Each symptom is rated based on frequency, severity, and caregiver distress. The NPI-X will be administered by trained raters through an interview with the caregiver.

MMSE

The Mini-Mental State Examination (MMSE) is a brief 30-point questionnaire used to screen for cognitive impairment and to track cognitive changes over time. It assesses orientation, registration, attention and calculation, recall, and language. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. The MMSE will be administered by trained raters.

8.3. Safety Assessments

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed with the participant in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- For blood pressure measurements, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure readings will be recorded.

8.3.3. Electrocardiograms

• Single 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.3.4. Clinical Safety Laboratory Tests

• See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

• The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

• Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

• All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

• If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

• All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

• If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy Testing

For women of childbearing potential, a serum or urine pregnancy test will be performed at screening and at each visit as indicated in the SoA. A negative pregnancy test result is required before the participant may receive the study intervention.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Xanomeline is considered to be a CNS-active intervention.

Patients with Alzheimer's disease may occasionally develop suicidal ideation or behavior.

Participants being treated with study intervention should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with study intervention should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior/intervention-emergent suicidal ideation and behavior will be monitored during the study using the Columbia-Suicide Severity Rating Scale (C-SSRS).

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

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

All AEs will be collected from the start of study intervention until the follow■up visit at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

See Section 8.4.5 for the time period for collecting pregnancy information and duration of follow-up of the pregnancy, if required.

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.8) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB/package insert or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

• Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators within 15 days.

8.4.5. Pregnancy

• Details of all pregnancies in participants able to give birth will be collected after the start of study intervention and until 30 days after the last dose of study intervention.

• If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the participant's pregnancy.

• While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

• Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

• The investigator will collect follow-up information on the participant, the pregnancy outcome, and the neonate. The information will be forwarded to the sponsor.

• Any poststudy pregnancy-related SAE in the mother or SAE in the newborn, if considered reasonably related to the study intervention by the investigator, will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

• Any participant who becomes pregnant while participating in the study will discontinue study intervention.

8.4.6. Cardiovascular and Death Events

Any cardiovascular events and deaths will be reported as SAEs and will be subject to expedited reporting to regulatory authorities if they meet the criteria for SUSARs.

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

The following disease-related events (DREs) are common in participants with Alzheimer's disease and can be serious/life threatening:

• Cognitive decline

• Behavioral disturbances

• Falls

• Weight loss

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded within the appropriate timeframe. These DREs will be monitored by an independent data monitoring committee on a routine basis.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.4.8. Adverse Events of Special Interest

The following adverse events are of special interest and will be subject to expedited reporting:

- Significant cholinergic side effects (severe nausea, vomiting, diarrhea, excessive sweating, hypersalivation, urinary urgency)
- Significant cardiovascular events (bradycardia, tachycardia, hypotension, hypertension, syncope)
- Severe skin reactions at the patch application site
- Neuropsychiatric symptoms (hallucinations, agitation, confusion)

8.4.9. Medical Device Deficiencies

Not applicable for this study.

8.5. Pharmacokinetics

Plasma samples of approximately 5 mL will be collected for measurement of plasma concentrations of xanomeline as specified in the SoA (Section 1.3).

A maximum of 2 samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of xanomeline. Each plasma sample will be divided into 2 aliquots (1 for PK and 1 for backup). Samples collected for analyses of xanomeline concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

Pharmacodynamic assessments are not planned for this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not applicable for this study.

8.10. Health Economics OR Medical Resource Utilization and Health Economics

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will:

- Include the reasons and duration of hospitalizations and emergency room visits and
- Exclude procedures, tests, and encounters mandated by the protocol.

The sponsor may use the collected data to conduct economic analyses.

9. Statistical Considerations

The analysis and reporting will be done on all data from all participants at the time the study ends.

The statistical analysis plan will be finalized prior to unblinding and database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints/estimands including primary and key secondary endpoints/estimands.

9.1. General Considerations

All statistical analyses will be performed using SAS version 9.4 or higher. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized using frequency counts and percentages.

The primary analysis population for efficacy will be the Full Analysis Set (FAS), which includes all randomized participants according to the treatment to which they were randomized (intention-to-treat principle). Safety analyses will be performed on the Safety Analysis Set (SAS), which includes all participants who received at least one dose of study intervention, according to the treatment actually received.

9.1.1. Decision Criteria/Statistical Hypotheses

The primary objective is to demonstrate that xanomeline TTS (50 cm^2, 75 cm^2, and 100 cm^2) is superior to placebo in improving cognitive function and global clinical status in patients with mild to moderate AD. Thus, the null hypotheses to be tested in relation to the primary estimands are as follows:

For ADAS-Cog (11):

- Null hypothesis: Xanomeline TTS is not different from placebo with respect to the change from baseline to Week 24 in ADAS-Cog (11) total score.
- Alternative hypothesis: Xanomeline TTS is different from placebo with respect to the change from baseline to Week 24 in ADAS-Cog (11) total score.

For CIBIC+:

- Null hypothesis: Xanomeline TTS is not different from placebo with respect to the CIBIC+ score at Week 24.
- Alternative hypothesis: Xanomeline TTS is different from placebo with respect to the CIBIC+ score at Week 24.

The null and alternative hypotheses corresponding to the secondary estimands are as follows:

For time course of effects on cognition:

- Null hypothesis: Xanomeline TTS is not different from placebo with respect to the change from baseline to Weeks 8 and 16 in ADAS-Cog (11) total score.
- Alternative hypothesis: Xanomeline TTS is different from placebo with respect to the change from baseline to Weeks 8 and 16 in ADAS-Cog (11) total score.

For time course of effects on global clinical status:

- Null hypothesis: Xanomeline TTS is not different from placebo with respect to the CIBIC+ score at Weeks 8 and 16.
- Alternative hypothesis: Xanomeline TTS is different from placebo with respect to the CIBIC+ score at Weeks 8 and 16.

For behavioral symptoms:

- Null hypothesis: Xanomeline TTS is not different from placebo with respect to the mean change from baseline in NPI-X score from Week 4 to Week 24.
- Alternative hypothesis: Xanomeline TTS is different from placebo with respect to the mean change from baseline in NPI-X score from Week 4 to Week 24.

9.1.2. Multiplicity Adjustment

A closed testing procedure that controls the family wise error rate in the strong sense at the overall 5% level will be applied. The statistical comparisons for the primary efficacy endpoints and the key secondary endpoints will be carried out in the hierarchical order as follows:

1. Xanomeline TTS 100 cm^2 vs. placebo for ADAS-Cog (11) at Week 24
2. Xanomeline TTS 100 cm^2 vs. placebo for CIBIC+ at Week 24
3. Xanomeline TTS 75 cm^2 vs. placebo for ADAS-Cog (11) at Week 24

4. Xanomeline TTS 75 cm² vs. placebo for CIBIC+ at Week 24
5. Xanomeline TTS 50 cm² vs. placebo for ADAS-Cog (11) at Week 24
6. Xanomeline TTS 50 cm² vs. placebo for CIBIC+ at Week 24
7. Xanomeline TTS 100 cm² vs. placebo for ADAS-Cog (11) at Week 16
8. Xanomeline TTS 100 cm² vs. placebo for CIBIC+ at Week 16
9. Xanomeline TTS 75 cm² vs. placebo for ADAS-Cog (11) at Week 16
10. Xanomeline TTS 75 cm² vs. placebo for CIBIC+ at Week 16
11. Xanomeline TTS 50 cm² vs. placebo for ADAS-Cog (11) at Week 16
12. Xanomeline TTS 50 cm² vs. placebo for CIBIC+ at Week 16
13. Xanomeline TTS 100 cm² vs. placebo for ADAS-Cog (11) at Week 8
14. Xanomeline TTS 100 cm² vs. placebo for CIBIC+ at Week 8
15. Xanomeline TTS 75 cm² vs. placebo for ADAS-Cog (11) at Week 8
16. Xanomeline TTS 75 cm² vs. placebo for CIBIC+ at Week 8
17. Xanomeline TTS 50 cm² vs. placebo for ADAS-Cog (11) at Week 8
18. Xanomeline TTS 50 cm² vs. placebo for CIBIC+ at Week 8
19. Xanomeline TTS 100 cm² vs. placebo for NPI-X from Week 4 to Week 24
20. Xanomeline TTS 75 cm² vs. placebo for NPI-X from Week 4 to Week 24
21. Xanomeline TTS 50 cm² vs. placebo for NPI-X from Week 4 to Week 24

This means that the statistical hypotheses are tested in the prespecified order at the same significance level of $\alpha = 0.05$ as long as all preceding hypotheses are rejected. Once a hypothesis is not rejected, subsequent hypotheses cannot be formally tested and therefore cannot be rejected.

9.1.3. Impact of Intercurrent Events Strategies

The primary estimand will use the treatment policy strategy for handling intercurrent events such as discontinuation of study intervention and use of rescue medication or change in background medication. This approach aims to estimate the effect of the treatment regardless of these intercurrent events, reflecting the effect as would be expected in clinical practice.

9.1.4. Handling of Missing Data

The primary analysis will use a Mixed Model for Repeated Measures (MMRM) approach for the ADAS-Cog (11) endpoint, which handles missing data under the missing at random (MAR) assumption. For the CIBIC+ endpoint, an Analysis of Covariance (ANCOVA) model will be used with multiple imputation for missing data.

Sensitivity analyses will be conducted to assess the robustness of the results to the missing data assumptions, including pattern mixture models and tipping point analyses.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set (FAS)	All randomized participants.
Safety analysis set (SAS)	All participants who are exposed to investigational intervention.

The full analysis set will be used to analyze endpoints related to the efficacy objectives and the safety analysis set will be used to analyze the endpoints and assessments related to safety.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

9.3. Analyses Supporting Primary Objective(s)

9.3.1. Primary Endpoint(s)/Estimand(s)

9.3.1.1. Definition of endpoint(s)

The primary efficacy endpoints are:

1. Change from baseline in ADAS-Cog (11) total score at Week 24

2. CIBIC+ score at Week 24

9.3.1.2. Main Analytical Approach

For the ADAS-Cog (11) endpoint, the primary analysis will use a Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment, visit, treatment-by-visit interaction, baseline ADAS-Cog (11) score, and stratification factors. An unstructured covariance matrix will be used to model the within-patient errors.

For the CIBIC+ endpoint, the primary analysis will use an Analysis of Covariance (ANCOVA) model with treatment and stratification factors as fixed effects and baseline MMSE score as a covariate. Multiple imputation will be used to handle missing data.

9.3.1.3. Sensitivity Analysis/Analyses

Sensitivity analyses will include:

- Pattern mixture models to assess the impact of different missing data mechanisms
- Tipping point analyses to determine how robust the results are to departures from the MAR assumption
- Per-protocol analyses excluding participants with major protocol deviations

9.3.1.4. Supplementary Analysis/Analyses

Supplementary analyses will include:

- Analyses using alternative methods for handling missing data
- Analyses adjusting for additional baseline covariates
- Responder analyses based on predefined thresholds for clinically meaningful change

9.4. Analyses Supporting Secondary Objective(s)

9.4.1. Analyses Supporting Secondary Objective label

For the time course of effects on cognition and global clinical status, the same analytical approaches used for the primary endpoints will be applied to the Week 8 and Week 16 timepoints.

For the NPI-X endpoint, an MMRM model similar to that used for the ADAS-Cog (11) endpoint will be used to analyze the mean change from baseline in NPI-X score from Week 4 to Week 24.

9.5. Analyses Supporting Tertiary/Exploratory/Other Objective(s)

Safety endpoints will be analyzed descriptively. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. The incidence of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation will be summarized by treatment group.

Changes from baseline in vital signs, ECG parameters, and clinical laboratory values will be summarized descriptively by treatment group and visit. Shift tables and listings of potentially clinically significant values will also be provided.

The incidence and severity of application site reactions will be summarized by treatment group.

9.6. Other Safety Analyses

Additional safety analyses will include:

- Time to first adverse event
- Duration of adverse events
- Relationship between adverse events and plasma concentrations of xanomeline
- Subgroup analyses of safety endpoints by age, sex, and baseline characteristics

9.7. Other Analyses

9.7.1. Other variables and/or parameters

Pharmacokinetic parameters will be summarized descriptively by treatment group and visit.

9.7.2. Subgroup analyses

Subgroup analyses of the primary efficacy endpoints will be performed for the following subgroups:

- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Baseline disease severity (mild [MMSE 18-23], moderate [MMSE 10-17])
- ApoE ε4 carrier status (carrier, non-carrier)
- Concomitant use of acetylcholinesterase inhibitors and/or memantine (yes, no)

9.8. Interim Analysis/Analyses

No interim analyses are planned for this study.

9.9. Sample Size Determination

Approximately 400 participants will be enrolled/randomized/assigned to investigational intervention. The sample size calculation is based on the primary efficacy estimand and its endpoint ADAS-Cog (11).

It is assumed that the mean change from baseline in ADAS-Cog (11) at Week 24 is -0.5 points in the placebo arm, -3.0 points in the xanomeline TTS 50 cm² arm, -4.0 points in the xanomeline TTS 75 cm² arm, and -4.5 points in the xanomeline TTS 100 cm² arm, with a common standard deviation of 6.0 points. Using a two-sided statistical test at a type-1 error level of 5%, a study with an overall sample size of N = 400 participants (100 per arm) will have over 90% power to detect a treatment difference between xanomeline TTS 100 cm² and placebo, approximately 85% power to detect a treatment difference between xanomeline TTS 75 cm² and placebo, and approximately 80% power to detect a treatment difference between xanomeline TTS 50 cm² and placebo.

For the CIBIC+ endpoint, assuming a mean score of 4.2 in the placebo arm, 3.7 in the xanomeline TTS 50 cm² arm, 3.5 in the xanomeline TTS 75 cm² arm, and 3.3 in the xanomeline TTS 100 cm² arm, with a common standard deviation of 1.2, the study will have approximately 90% power to detect a treatment difference between xanomeline TTS 100 cm² and placebo, approximately 85% power to detect a treatment difference between xanomeline TTS 75 cm² and placebo, and approximately 75% power to detect a treatment difference between xanomeline TTS 50 cm² and placebo.

The additional assumptions for the power calculation relating to intercurrent events are as follows: a 20% discontinuation rate by Week 24 and a 10% rate of rescue medication use or change in background medication.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

• This study will be conducted in accordance with the protocol and with the following:

• Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.

• Applicable ICH Good Clinical Practice (GCP) guidelines.

• Applicable laws and regulations.

• The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before implementation.

• Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

• Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

• The investigator will be responsible for the following, as applicable:

• Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

• Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

• Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies conducted in the EU, and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

• The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or their legally authorized representative and answer all questions regarding the study.

• Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data

protection requirements, where applicable, and the IRB/IEC or study center.

• The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

• Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

• A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Recruitment strategy

Participants will be recruited from memory clinics, neurology practices, and other healthcare settings that treat patients with Alzheimer's disease. Recruitment strategies may include:

• Referrals from healthcare providers

• Review of clinic databases for potentially eligible patients

• Advertisements in local media

• Community outreach events

• Patient advocacy group partnerships

All recruitment materials will be approved by the IRB/IEC before use.

10.1.5. Data Protection

• Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets 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 must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

• The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by

appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Committees Structure

10.1.6.1. Data Monitoring Committee

A data monitoring committee has been appointed for this study. The data monitoring committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The data monitoring committee will review safety data periodically throughout the study. The committee will also review efficacy data if a pre-specified interim analysis is conducted. The committee will make recommendations to the sponsor regarding the continuation, modification, or termination of the study based on the observed benefits or adverse effects of the study intervention.

10.1.7. Dissemination of Clinical Study Data

Study participants will be provided the option of receiving their individual study data. Management of dissemination and process for providing this option may be found in the study data management or individual participant data return plan in accordance with sponsor policies, laws, and regulations.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the study reference manual.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be predefined in the monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan contracts.

• The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

• The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

• Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study 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. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

• Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

• Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

• Definition of what constitutes source data and its origin can be found in the source data acknowledgment or monitoring guidelines.

• The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

• The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

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

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

Study/Site Termination

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

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

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table X will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study

intervention decision or response evaluation, the results must be recorded.

• Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

• Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table X: Protocol-required Safety Laboratory Tests

MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes White blood cell (WBC) count with differential: - Neutrop
Glucose (nonfasting) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Tota
e by dipstick Microscopic examination (if blood or protein is abnormal)
f childbearing potential)
s, cannabinoids and benzodiazepines) Serology (hepatitis B surface antigen HBsAg, and hepatitis C virus antibody)

NOTES:

Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver Event Stopping Criteria and Appendix 6: Liver Safety: Suggestions and Guidelines for Liver Events. All events of ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT or AST ≥3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to sponsor in an expedited manner.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition

• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

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

Events not Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

a. Results in death

b. Is life threatening

- The term life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.

• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

• **Mild**: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

• **Moderate**: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

• **Severe**: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

• A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

• For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

• The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

• The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

• The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

• New or updated information will be recorded in the originally submitted documents.

• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

• The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.

• If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

• The site will enter the SAE data into the electronic system as soon as it becomes available.

• After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the sponsor/medical monitor/SAE coordinator by telephone.

• Contacts for SAE reporting can be found in the study reference manual.

SAE Reporting to the Sponsor via Paper Data Collection Tool

• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor or the SAE coordinator.

• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

• Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

• Contacts for SAE reporting can be found in the study reference manual.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment period and for at least 30 days after the last dose of study intervention:

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom.
- Male participants must not donate sperm for the duration of the study and for at least 30 days after the last dose of study intervention.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below:

Table: Highly Effective Contraceptive Methods

ntraceptive Methods That Are User Dependent	Failure rate of <1% per year when used consis
nd progestogen-containing) hormonal contraception associated with inhibition of ovulation	Oral, intravaginal, transdermal
onal contraception associated with inhibition of ovulation	Oral, injectable
ontraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an	
ctive method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The relial	

NOTES:

1. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

2. Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method.

Pregnancy testing will be performed in WOCBP at the timepoints specified in the SoA. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with an irregular menstrual cycle. The participant must be referred to a gynecologist if pregnancy is suspected.

10.5. Appendix 5: Genetics

Genetics are not evaluated in this study.

10.6. Appendix 6: Liver Safety: Suggestions and Guidelines for Liver Events

Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm

If ALT or AST > 3 × ULN and total bilirubin > 2 × ULN (> 35% direct bilirubin) or INR > 1.5:

1. Report as an SAE.
2. Complete liver event CRF.
3. Perform liver event follow-up assessments.
4. Withdraw from study intervention and continue follow-up.

If ALT or AST > 8 × ULN:

1. Report as an SAE.
2. Complete liver event CRF.
3. Perform liver event follow-up assessments.
4. Withdraw from study intervention and continue follow-up.

If ALT or AST > 5 × ULN but < 8 × ULN persists for ≥ 2 weeks:

1. Report as an SAE.
2. Complete liver event CRF.
3. Perform liver event follow-up assessments.
4. Withdraw from study intervention and continue follow-up.

If ALT or AST > 5 × ULN but < 8 × ULN and cannot be monitored weekly for ≥ 2 weeks:

1. Report as an SAE.
2. Complete liver event CRF.
3. Perform liver event follow-up assessments.
4. Withdraw from study intervention and continue follow-up.

If ALT or AST > 3 × ULN but < 5 × ULN and total bilirubin > 1.5 × ULN but < 2 × ULN:

1. Report as an SAE.
2. Complete liver event CRF.
3. Perform liver event follow-up assessments.
4. Withdraw from study intervention and continue follow-up.

Liver Event Follow-up Assessments

For all liver events:

- Physical examination
- Liver event symptom assessment
- Repeat liver chemistries and serum creatinine within 24-48 hours
- Complete blood count with differential
- Viral hepatitis serology (hepatitis A, B, C, and E)
- Blood sample for PK analysis (if applicable)
- Appropriate diagnostic imaging (e.g., ultrasound, MRI)

10.7. Appendix 7: Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

Not applicable for this study.

10.8. Appendix 8: Country-specific Requirements

[To be provided by Sponsor as applicable]

10.9. Appendix 9: Protocol Amendment History

Amendment [amendment number]: (date)

This amendment is considered to be substantial/nonsubstantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament.

Overall Rationale for the Amendment

[Not applicable for original protocol]

11. References

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