

Medical Inclusion and Exclusion Criteria for the PIA-Study

Inclusion Criteria	<p>Patients must satisfy all of the following criteria to be enrolled in the study:</p> <ol style="list-style-type: none">1. Must have given written informed consent before any study-related activities are carried out and must be able to understand the full nature and purpose of the trial, including possible risks and adverse effects.2. Adult males and females, 18 to 84 (inclusive) at screening.3. Diagnosis of Alzheimer's Disease confirmed by:<ol style="list-style-type: none">a. A positive amyloid biomarker (PET scan) indicative of AD pathology,b. Mini-mental-state examination (MMSE) score of 22 or greater,c. Free and cued selective reminding test (FCSRT) cueing index of 0.79 or lessd. Clinical Dementia Rating (CDR) global score of 0.5 or 1.0.4. Able to take oral medications and willing to record daily adherence to the study drug.5. QT interval corrected using the Fridericia method (QTcF) \leq 450 msec for males and \leq 460 msec for females at screening and on Day 1, prior to dose administration (<i>the mean of the two time points will be used to determine eligibility</i>).6. Evidence of adequate hepatic function at screening, as defined by the following:<ol style="list-style-type: none">a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN) andb. Total bilirubin $\leq 1.5 \times$ ULN.7. Evidence of adequate renal function, as defined by a calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault equation or 24-hour urine collection with plasma and urine creatinine concentrations respectively.8. Adequate coagulation laboratory assessments (i.e. results within normal ranges, per local laboratory definition) at screening.9. Lipids (total cholesterol, HDL and LDL) must be within $< 1.5 \times$ the upper limit of normal for the local laboratory reference range at the screening visit10. FBC must be within $< 1.5 \times$ the upper limit of normal for the local laboratory reference range at the screening visit11. Female volunteers:<ol style="list-style-type: none">a. Must be of non-childbearing potential (i.e., surgically sterilised [hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before the screening visit]) or postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause at the screening visit), orb. If of childbearing potential, must agree not to donate ova, not to attempt to become pregnant and, if engaging in sexual intercourse with a male partner, must agree to the use of acceptable forms of highly effective contraception from the time of signing the consent form until at least 30 days after the last dose of the study drug.12. Male volunteers:
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	<ul style="list-style-type: none"> a. Engaging in any sexual intercourse, including those who are infertile and do not produce sperm (e.g. post-vasectomy), must abstain from unprotected sex until the End of Study visit or equivalent i.e. 4 days after last dose b. Must agree to abstain from sperm donation, and if engaging in sexual intercourse with a female of child bearing potential must agree to the use of an acceptable form of highly effective contraception (refer to Appendix 5) from the time of signing the consent form until at least 90 days after the last dose of study drug. <p>13. Have suitable venous access for blood sampling.</p> <p>14. Be willing and able to comply with all study assessments and adhere to the protocol schedule and restrictions.</p> <p>15. A study partner (partner/spouse/carer) consents to the minimum requirements:</p> <ul style="list-style-type: none"> a. will attend at least one screening visit b. will be available via phone or in person to provide information to the study as required
<p>Exclusion Criteria</p>	<p>A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:</p> <ul style="list-style-type: none"> 1. Recorded number of falls in previous 12 months and during trial. Participants who report multiple falls with potential loss of consciousness will be excluded 2. History of QTc-induced prolongation and willingness to limit use of over-the-counter, or prescription medicines (e.g. anti-histamines) known to prolong QTc interval. Corrected QT interval using Bazett's formula (QTcB) interval > 450 msec for males, or 470 msec for females, as detected by ECG and confirmed by physician. Participants who have a history of QTc-induced prolongation and are unwilling to limit use of medication will be excluded. 3. Evidence of abnormal cardiac function as defined by any of the following: <ul style="list-style-type: none"> a. Myocardial infarction within 6 months of Cycle 1, Day 1 b. Symptomatic congestive heart failure (New York Heart Association > Class II) c. Unstable angina d. Atrial fibrillation including paroxysmal atrial fibrillation. e. Frequent multifocal ventricular arrhythmia 4. Unable to swallow oral medications. 5. Gastrointestinal conditions that, in the opinion of the Investigator, could affect the absorption of study drug. 6. Use of any prescription or non-prescription (including herbal) medications, or consumption of foods known to be strong QT prolongation within 7 days prior to the first administration of Lorelco™ and for the duration of the study . These include (but are not limited to): <ul style="list-style-type: none"> a. <i>Medications</i> b. With significant central anticholinergic effects, c. Sedatives, d. Antiparkinsonian medications that cannot be stopped prior to study entry,

	<p>e. Any investigational treatment for AD</p> <ol style="list-style-type: none"> 7. Current diagnosis of cancer (within 5 years) and/or undergoing chemotherapy, 8. Significant head injury within 5 years 9. Electrolyte imbalance (e.g. on high steroids, pituitary tumours, and Addison disease) 10. Hypokalaemia, hypomagnesaemia and hypocalcaemia 11. They have other neurologic or psychiatric diagnosis that in the opinion of the investigator could interfere with cognitive function, 12. Major surgery is planned during the conduct of the trial, or a clinical event has occurred in the six months preceding study inclusion that may compromise ability to participate for the duration of the study, 13. A FAZEKAS score >1, or evidence of stroke, 14. Current diagnosis with a psychiatric disorder, or taking psychotropic medications, 15. Willing and able to undergo Magnetic Resonance Imaging (MRI) 16. Other excluded medications will be those that are; <ul style="list-style-type: none"> • Specifically contraindicated with ProbucoI, based on historic clinical indications for the treatment of cardiovascular disease. Stable use (for at least 3 months) of cholinesterase inhibitors and memantine will be allowed. • Patients on high dose loop-diuretics or thiazide diuretic medications, will be excluded if taking maximum dose of furosemide or Bendroflumethiazide 17. Self-reported human immunodeficiency virus (HIV-1 or HIV-2), hepatitis B (HBsAg) or hepatitis C virus (HCV). 18. Any inflammatory or chronic pain condition that necessitates regular use of opiates/opioids, 19. Major surgery within 28 days of Cycle 1, Day 1, or minor surgical procedures within 7 days of Cycle 1, Day 1. <i>Exception: no waiting period applies following port-a-cath placement for venous access.</i> 20. For women of childbearing potential, a positive pregnancy test at screening, or on Day 1, prior to dose administration. 21. Pregnant or breast-feeding (or planning to breastfeed) while on study through 15 days after the last dose of study drug. 22. Hypersensitivity or other clinically significant reaction to the study drug or its inactive ingredients. 23. Known substance abuse or medical, psychological, or social conditions that, in the opinion of the Investigator, may interfere with the patient's participation in the clinical study or evaluation of the clinical study results. 24. Any other condition or prior therapy that in the opinion of the Investigator would make the patient unsuitable for this study, including inability to cooperate fully with the requirements of the study protocol or likelihood of noncompliance with any study requirements
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