TITLE PAGE

PROTOCOL NUMBER	**PIA-2020**	
STUDY TITLE	A Double-Blind, Placebo Controlled, Randomised Phase II Trial of Probucol in Alzheimer's Disease (PIA-Study): The Impact on Cognition	
PHASE	2	
INVESTIGATIONAL AGENT (*Active*):	Probucol (Lorelco™)	
ROUTE OF ADMINISTRATION:	Oral administration	
SPONSOR:	Curtin University Kent St, Bentley WA 6102 AUSTRALIA	Curtin University
SPONSOR REPRESENTATIVE	Professor John Mamo Curtin Health Innovation Research Institute	
PROTOCOL VERSION:	Version 4	
PROTOCOL DATE:	06 October 2021	

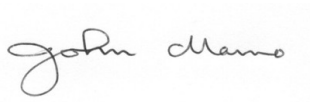
CONFIDENTIALITY STATEMENT

Information contained in this protocol should not be disclosed, other than to those directly involved in the execution or ethical review of the study, without written authorisation from Curtin University. It is, however, permissible to provide information to a volunteer in order to obtain consent.

SPONSOR SIGNATURE PAGE

Study Title:

A Double-Blind, Placebo Controlled, Randomised Phase II Trial of Probucol in Alzheimer's Disease (PIA-Study): The Impact on Cognition



06/10/21

Signature of Sponsor Representative ***Date***

John Mamo

Printed Name of Sponsor Representative

Professor of Health Sciences, Director, Curtin Health Innovation Research Institute, Curtin University.

Sponsor Representative Role/Designation

By my signature, I confirm that I have reviewed this protocol and find its content to be acceptable.

1 PROTOCOL SYNOPSIS

Study Title	A Double-Blind, Placebo Controlled, Randomised Phase II Trial of Probucol in Alzheimer's Disease (PIA-Study): The Impact on Cognition
Study Number	PIA-2020
Phase	Phase II
Number of Clinical Sites	Up to 2 sites within Australia
Study Population	Subjects with mild to moderate Alzheimer's Disease Patient-specific selection criteria apply, as described in the study eligibility criteria.
Patient Number	Up to 314 patients are planned to be recruited
Study Treatment	Lorelco™ Tablets: 250 mg will be administered in this study. Lorelco™ will be over-encapsulated inside an opaque capsule shell and backfilled with Microcrystalline cellulose. Intermediate doses may also be evaluated at the discretion of the Sponsor and in consultation with the Safety Review Committee (SRC). Placebo: Matched capsules
Route of Administration	Oral
Number of doses per treatment	Week 1 and 2: One placebo capsule taken in the morning, with food. Week 3: One 250 mg Lorelco™ (or matching placebo) taken in the morning, with food. Week 4 to 104: One 250 mg Lorelco™ (or matching placebo) taken in the morning, with food. One 250 mg Lorelco™ (or matching placebo) taken in the evening, with food.
Study Duration	The study timeframe will include up to a 56-day screening period, 2 week placebo week treatment period and a 104 week active or placebo treatment period, and a follow-up visit 4 weeks from the last dose of study treatment. Patients will continue on the study unless they have unacceptable adverse events, unacceptable QT/QTc interval prolongation, they withdraw informed consent, or are withdrawn from the study. In the event of strong clinical benefit, and at the discretion of the study doctor, a participant may be reinstated in the study 4 weeks after discontinuation of the participant due to AE. This will be evaluated on a case by case basis. Regardless of perceived benefit, participants cannot continue probucol at the

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Study Title:

A Double-Blind, Placebo Controlled, Randomised Phase II Trial of Probucol in Alzheimer's Disease (PIA-Study): The Impact on Cognition

Roger Clarnette — 20 October 2021

Signature of Principal Investigator — ***Date***

Roger Clarnette

Printed Name of Principal Investigator

Institution Name: Australian Alzheimer's Research Foundation

By my signature, I confirm that I have read the protocol, I understand it, and I agree to personally conduct and supervise the conduct of this study in compliance with the protocol, Human Research Ethics Committees (HRECs) procedures, instructions from Curtin University Therapeutics Pty Ltd, the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice Guidelines, and local regulations governing the conduct of clinical studies.

	end of the study as Lorelco™ is not approved for use in Australia. If strong clinical support is identified in the study, this will support effectiveness and phase III trials.	
Study Confinement periods	There are no scheduled confinement periods for this study, however if patients experience any clinically significant adverse events (AEs) during the study, they may be admitted to the clinical facility for further observation at the discretion of the Principal Investigator (PI). Participants will be required to attend the clinic at screening, and at Week(s): 3, 4, 5, 15, 26, 39, 52, 65, 78, 91, 104 and approximately 4 weeks following the end of the study (Week 108) In addition to the above, patients will also be required to an end of study visit 4 weeks after their last dose of study drug.	
Study Objectives and Endpoints		
	Objective(s)	Endpoint(s)
Primary	To evaluate the preliminary efficacy of 250 mg BID Lorelco™ on cognitive performance in Alzheimer's patients over a 102 week treatment period	Cognitive performance parameters include (but are not limited to): • Cognitive Subscale test (ADAS-Cog)
Secondary	To evaluate : • cerebral amyloid abundance • regional volumetric changes in the brain in the brain of Alzheimer's Disease patients treated with Lorelco™ over a 102 week treatment period.	PET Scan • visual assessment of amyloid load • quantitative assessment of amyloid burden MRI Scan • volumetric changes in the brain • cerebral amyloid abundance
	To evaluate improvement or maintenance of Quality of Life parameters in patients with Alzheimer's Disease	Quality of life parameters to be assessed include (but are not limited to): • Alzheimer's Disease Co-operative Study Mild Cognitive Impairment Activities of Daily Living scale (ADCS-MCI-ADL24) • Depression Anxiety Stress Scale (DASS-21)
	To assess the safety and tolerability of Lorelco™ in patients with Alzheimer's Disease	Safety and tolerability endpoints include: • Incidence, type and severity of AEs • Dose-limiting toxicities (DLTs) • Changes from baseline in: • electrocardiogram (ECG)

		parameters • vital sign measurements • body weight • physical examination findings • clinical laboratory parameters

Inclusion Criteria	Patients must satisfy all of the following criteria to be enrolled in the study: 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: 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 less OR free recall score ≤17 d. 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) ≤ 450 msec for males and ≤ 460 msec for females at screening and on Day 1, prior to dose administration *(the mean of the two time points will be used to determine eligibility)*. 6. Evidence of adequate hepatic function at screening, as defined by the following: a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN)and b. Total bilirubin ≤1.5 × 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 x the upper limit of normal for the local laboratory reference range at the screening visit 10. FBC must be within < 1.5 x the upper limit of normal for the local laboratory reference range at the screening visit 11. Female volunteers: 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), or

	b. 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 (refer to Appendix 5) from the time of signing the consent form until at least 30 days after the last dose of the study drug. 12. Male volunteers: 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. 13. Have suitable venous access for blood sampling. 14. Be willing and able to comply with all study assessments and adhere to the protocol schedule and restrictions. 15. A study partner (partner/spouse/carer) consents to the minimum requirements: 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
Exclusion Criteria	A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study: 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: 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. Unstable atrial fibrillation including paroxysmal atrial fibrillation. Medicated, stable atrial fibrillation will be assessed by the study doctor on a case-by-case basis 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 QTprolongation within 7 days prior to the first administration of Lorelco™ and for the duration of the study . These include (but are not limited to): a. *Medications:* See APPENDIX 7. b. With significant central anticholinergic effects, c. Sedatives, d. Antiparkinsonian medications that cannot be stopped prior to study entry, e. Any investigational treatment for AD 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. 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; • Specifically contraindicated with Probucol, 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. *Exception: no waiting period applies following port-a-cath placement for venous access.* 20. For women of childbearing potential, a hCG pregnancy test > 5 U/L 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
Overall Study Design Description	This is a Phase 2, randomised, double blind, placebo-controlled parallel group study in adults with mild to moderate AD. The study will assess the efficacy, safety and tolerability of the treatment of Alzheimer's disease subjects with Lorelco™. After consenting to participate in the study, screening procedures will occur between Days -56 and -1. All subjects must have measurable mild or moderate Alzheimer's disease, and accordingly screening procedures will include: • A positive amyloid biomarker (PET scan) indicative of AD pathology, • Mini-mental-state examination (MMSE) score of 22 or greater, • Free and cued selective reminding test (FCSRT) cueing index of 0.79 or less OR free recall score ≤17 • Clinical Dementia Rating (CDR) global score of 0.5 or 1.0. • A study partner (partner/spouse/carer) consents to the minimum requirements: o Study partner will attend *at least one* screening visit o Study partner will be available via phone or in person to provide information to the study as required Eligible subjects will be randomized in a 1:1 (active:placebo) ratio and return to the study unit on Day 1. Subjects will be dosed as: • Week 1 and 2: 1 x placebo taken in the morning, with food • Week 3: 1 x 250 mg Lorelco™ (or matching placebo) taken in the morning, with food. • Week 4 – 104: 1 x 250 mg Lorelco™ (or matching placebo) taken in the morning, with food. 1 x 250 mg probucol (or matching placebo) taken in the evening, with food.
Duration of Study and Dose Administration Stopping Rules	Patients may continue to receive study medication until week 104 unless evidence of unacceptable toxicities, they withdraw consent or are withdrawn. The primary study analysis will occur when target enrolment is complete, and each patient either completes 104 weeks on study, or withdraws. If treatment during the study is interrupted, Lorelco™ may be reinitiated. At the discretion of the principal investigator, a participant may be reinstated in the study 4 weeks after discontinuation of the participant. This will be evaluated by the Investigator and the DSMB on a case by case basis. All participants will take part in a safety evaluation 4 weeks following discontinuation.

Study Assessments	
Safety and Tolerability	• Medical history • Evaluation of any on-study AEs and concomitant medication use • Height and weight • Physical examination • Vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature) • 12-lead ECGs • Analysis of laboratory safety markers (including haematology, serum chemistry, coagulation , lipid analysis and urinalysis)
Efficacy	Primary cognitive assessments will be the: • Alzheimer's Disease Assessment Scale-Cognitive Subscale test (ADAS-Cog) Secondary efficacy assessment will be the: • Alzheimer's Disease Co-operative Study Mild Cognitive Impairment Activities of Daily Living (ADCS-MCI-ADL24) • Depression Anxiety Stress Scale (DASS-21) PET Scan • visual assessment of amyloid load • quantitative assessment of amyloid burden MRI Scan • volumetric changes in the brain • cerebral amyloid abundance
Statistical Analysis	
Overview	Analysis of all primary and secondary endpoints contrasting Lorelco™ and placebo, after adjusting for covariates, will use mixed effects-regression with 'random' intercepts and slopes (as has been used for power calculations). Mean differences and associated 95% confidence intervals will be presented for the 'fixed' effect Lorelco™ treatment.
Safety and Tolerability	The secondary analysis will assess the safety and tolerability of Lorelco™ in patients with mild to moderate Alzheimer's disease using the safety population. Treatment emergent adverse events (TEAEs) will be grouped by Medical Dictionary of Regulatory Activities (MedDRA) system organ class and preferred term and summarized by presenting the number and percentage of patients who experience each AE and the number of AEs. Summaries by severity (graded according to the NCI-CTCAE v5.0 [or higher]) and relationship to study drug will be provided for all TEAEs. Where applicable, laboratory test results will be graded and summarized according to the NCI-CTCAE v5.0 (or higher). The actual values and changes from baseline at each post-baseline time point for clinical laboratory parameters, vital signs and ECG parameters will be summarized by visit and timepoint (where applicable).
Pharmacodynamics	Pharmacodynamic marker parameters – observed data and change from baseline – will be summarized using descriptive statistics and graphs (mean ± SEM) per time interval as appropriate.

Efficacy	The primary analysis was an intention-to-treat analysis of all randomized participants. Data will be analysed using both Generalised Estimating Equations (GEE) and Bayesian Analysis. The analysis of primary endpoints will use linear mixed-effects models, with random slopes and intercepts. The Alzheimer's Disease Assessment Scale's cognitive subscale (ADAS-Cog) is the standard primary cognitive outcome measure for evaluating treatments in clinical trials of mild-to-moderate AD. The scoring methodology ADAS-Cog as proposed by Verma et al. will be utilised as it significantly improves the sensitivity of the ADAS-Cog in measuring progression of cognitive impairment in clinical trials focused in the mild-to-moderate AD stage19. Further analysis investigating the relationship between change scores (post-minus pre-intervention scores) for the primary ADAS-Cog with MRI volumes (total GM, hippocampus, and medial temporal lobe volumes) and specific blood biomarkers (eg: plasma lipoprotein-Aβ) will be considered using Pearson (or Spearman where appropriate) correlation analysis. For all other correlations between recorded variables that lack an a priori hypothesis, control of statistical errors will be carried out using Holm-Sidak corrections for multiple comparisons. If Lorelco™ treatment is successful, a directed acyclic graph Bayesian network analysis will be carried out a posteriori on variables identified to be significant predictors of either GM arrest or neuropsychological performance to better elucidate mechanisms of the effect of Lorelco™. Greedy equivalence search will be used to identify statistical conditional dependencies between variables and directionality will be estimated using the linear, non-Gaussian, acyclic causal models (LiNGAM) approach20, 21. Goodness of fit will be estimated using a $\chi 2$ test contrasting the identified model against a saturated model. In addition to Bayesian analyses, the traditional General Linear Model analysis will also be utilised to compare Lorelco™ to placebo, after adjusting for covariates. The Generalized Estimating Equations method, which extends the generalized linear model to allow for analysis of repeated measurements or other correlated observations, will also be utilised. Mean difference and associated 95% confidence intervals will be presented. Data will be analysed using Stata Version 16.

2 TABLE OF CONTENTS

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2.1 List of In-Text Figures

2.2 List of In-Text Tables

3 LIST OF ABBREVIATIONS AND TERMS

ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
CMI	Consumer medicine information
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
CRO	Clinical research organisation
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CTN	Clinical trial notification
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End of study
FBC	Full blood count
GCP	Good clinical practice
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
HREC	Human research ethics committee
ICF	Information and informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational product
ISF	Investigator site file
MedDRA	Medical dictionary for regulatory activities
MM	Medical monitor
MRI	Magnetic resonance imaging
PI	Principal investigator
QTcF	Corrected QT interval using Fridericia's formula
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SEM	Standard error of the mean
SoA	Schedule of assessments
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event

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TGA	Therapeutic goods association
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child-bearing potential

Lam V, *et al. BMJ Open* 2022; 12:e058826. doi: 10.1136/bmjopen-2021-058826

4 INTRODUCTION

4.1 Background Information

Presently there is no effective treatment to slow cognitive decline in Alzheimer's disease, the most common cause of dementia in low, middle and high income nations with an ageing population. New disease modifying treatments are urgently required. Worldwide well-resourced efforts have been unable to generate a single disease modifying strategy. This substantive unmet need demands further investment.

Several recent bio-epidemiological studies show that systemic measures of amyloid beta (Aβ) in blood positively correlate with cerebral amyloid burden and cognitive decline in Alzheimer's disease (AD)[1]. A causal association is suggested based on the findings that blood measures of Aβ isoforms discriminate with a high degree of accuracy, subjects who go on to develop AD decades before onset of disease[2]. However, presently the mechanism(s) by which peripheral Aβ metabolism might exacerbate AD risk are not well understood.

Amyloid-beta is the primary protein found in toxic brain deposits in AD, however in the periphery, amyloid-beta is a regulating protein moiety of lipoproteins, which transport fats in the aqueous environment of blood.

Pre-clinical studies have been developed using a new strain of genetically engineered mice that produce human amyloid-beta, restricted exclusively to liver (HSHA strain). The HSHA mice like humans, secrete amyloid tightly associated with nascent triglyceride-rich-lipoproteins (the precursor lipoprotein of low-density-lipoprotein, commonly considered in cardiovascular disease). Preclinical studies in the HSHA mice have discovered that exaggerated vascular exposure to lipoprotein-human-amyloid results in substantial neurovascular insult. There is increased blood-derived cerebral amyloid abundance in HSHA mice associated with substantial brain atrophy indicated in regions critical to memory and indeed, the HSHA mice develop marked cognitive deficits compared to aged-matched controls.

We have also discovered that probucol (an historic cholesterol lowering drug used to reduce risk for heart disease) profoundly suppresses lipoprotein-amyloid secretion[3]; promotes lipoprotein-amyloid clearance[4]and moreover, probucol prevents capillary dysfunction (increased permeability and parenchymal extravasation of plasma proteins[5]. In addition, probucol is a potent modulator of hemoxygenase[6] and a potent antioxidant[7], which may explain its profound attenuation of neurovascular inflammation. The synergistic properties of probucol in reducing vascular exposure to potentially toxic blood lipoprotein-amyloid concomitant with potent suppression of inflammation along with evidence that it supports cognitive function in HSHA mice, provides an exceedingly strong rationalization to test this drug clinically. Indirect support for the proposition of pleiotropic effects of probucol is suggested by the ongoing Probucol Trial for Secondary Prevention of Atherosclerotic Events in Patients with Prior Coronary Heart Disease (PROSPECTIVE) trial, a prospective study designed to test the hypothesis that the addition of Probucol to other lipid-lowering drugs will prevent cerebro- and cardiovascular events in patients with prior coronary events and high LDL cholesterol levels[8].

There have now been approximately 400 clinical trials completed in AD with none targeting peripheral (blood) lipoprotein-amyloid metabolism, or cerebral capillary integrity. There are no studies to date which have demonstrated significant efficacy, or sparing of cognitive

performance in AD. Fortuitously, widespread historic clinical use of probucol demonstrates good tolerability with minimal side effects, or adverse events reported. Hence, rapid translational opportunities may be realized, if efficacy is established.

4.2 Clinical Experience

Probucol clinical trials commenced in the United States in 1977. Dow Chemical Japan, Otsuka Pharmaceutical and Daiichi Pharmaceutical confirmed safety in non-clinical studies and thereafter, also commenced clinical trials in 1984(A1).

Concerns were raised regarding the probucol-induced reduction of serum high-density-lipoprotein (HDL)-cholesterol and potential QT prolongation[9]. Concomitant with the evolution of alternative cholesterol lowering agents, Western countries ceased use of probucol in 1995. However, probucol has remained in use in Japan and other countries including South Korea and China. More recent clinical studies support the concept that probucol should be reconsidered as a drug for coronary heart disease risk-reduction[9].

This is a FIH trial for Probucol in the treatment of subject with mild to moderate Alzheimer's Disease.

Collectively, results of the *in vitro* and *in vivo* preclinical pharmacology studies support the assessment of Lorelco™ as a disease modifying treatment for subjects with mild to moderate with Alzheimer's disease. It is hypothesised that Lorelco™ will slow the rate of cognitive decline in AD by reducing capillary insult to lipoprotein-amyloid beta; suppressing parenchymal extravasation of lipoprotein-amyloid beta and attenuating neurovascular inflammation.

4.3 Justification for Starting Dose Level and Regimen

The recommended and maximal dose for lowering blood cholesterol is up to 1000mg daily given in two divided doses of 500 mg each with the morning and evening meals. The PIA-study will provide probucol at 250mg b.i.d as recommended in A1 and consistent with recent clinical trials.

The two week initial placebo period will allow for implementation and retraining to assist with dose compliance, without giving participants the intervention drug.

The dose level and regime begins at 250 mg a day (Week 3) to monitor for gastrointestinal safety events (as described in section 6.1).

4.4 Risk Assessment and Guidance for Investigators

Prolongation of the QT interval can occur in patients on probucol. Clinical trials by Yamashita[10] and Kang[11] reported significantly more prolonged QT interval adverse events in individuals taking probucol (Lorelco™), compared to controls. While drug-induced prolonged QT interval can be associated with significant adverse side effects such as ventricular arrhythmia (torsades de pointes), studies involving the use of 500 mg of Probucol daily, reported probucol-induced prolonged QT interval was not associated with, or increased the incidence of, ventricular arrhythmias. Furthermore, Walldius[12] reported that there was no significant difference in cardiovascular clinical events between individuals taking probucol and controls. No malignant arrhythmias or torsades de pointes were reported for either group. The absence of arrhythmias may be due to strict prolonged QT/QTc interval exclusion

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criteria. While there is no consensus on upper limit corrected QT/QTc interval values, many studies adopt an absolute QT/QTc interval prolongation of > 500ms. This reduces the risk of ventricular arrhythmia, as participants are discontinued prior to prolonged QT intervals associated with arrhythmia.

While QT prolongation by probucol may not enhance the occurrence of lethal ventricular arrhythmias, studies have identified several clinical risk factors for drug-induced arrhythmias, including probucol. These include;

- Cardiac factors (including congenital long QT syndrome, family history of sudden cardiac death, bradycardia)
- Myocardial hypertrophy
- Heart failure
- Liver disease
- Thyroid Dysfunction
- Renal or hepatic impairment

The above clinical risk factors should be considered prior to treatment with probucol[13].

Further information regarding Lorelco™ is available in the Investigator's Brochure.

Lam V, *et al. BMJ Open* 2022; 12:e058826. doi: 10.1136/bmjopen-2021-058826

5 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are provided in Table 2, below.

Table 1. Study Objectives and Endpoints for Study PIA-2020

Objective(s)	Endpoint(s)
Primary	
• To evaluate the preliminary efficacy of 250 mg BID Lorelco™ on cognitive performance in Alzheimer's patients over a 102 week treatment period	Cognitive performance parameters include (but are not limited to): • Cognitive Subscale test (ADAS-Cog)
Secondary	
To evaluate : • cerebral amyloid abundance • regional volumetric changes in the brain in the brain of Alzheimer's Disease patients treated with Lorelco™ over a 102 week treatment period.)	PET Scan • visual assessment of amyloid load • quantitative assessment of amyloid burden MRI Scan • volumetric changes in the brain cerebral amyloid abundance
To evaluate improvement or maintenance of Quality of Life parameters in patients with Alzheimer's Disease	Quality of life parameters to be assessed include (but are not limited to): • Alzheimer's Disease Co-operative Study Mild Cognitive Impairment Activities of Daily Living scale (ADCS-MCI-ADL24) • Depression Anxiety Stress Scale (DASS-21)
To assess the safety and tolerability of Lorelco™ in patients with Alzheimer's Disease	Safety and tolerability endpoints include: • Incidence, type and severity of AEs • Dose-limiting toxicities (DLTs) • Changes from baseline in: • electrocardiogram (ECG) parameters • vital sign measurements • body weight • physical examination finding • clinical laboratory parameters

6 STUDY DESIGN

6.1 Design Type and Description

This is a Phase 2, randomised, double blind, placebo-controlled parallel group study in adults with mild to moderate AD.

The study will assess the efficacy, safety and tolerability of the treatment of Alzheimer's disease in approximately 300 subjects with Lorelco™.

After consenting to participate in the study, screening procedures will occur between Days -24 and -1. All subjects must have measurable mild or moderate Alzheimer's disease, and accordingly screening procedures will include:

- A positive amyloid biomarker (PET scan) indicative of AD pathology,
- Mini-mental-state examination (MMSE) score of 22 or greater,
- Free and cued selective reminding test (FCSRT) cueing index of 0.79 or less OR free recall score ≤17
- Clinical Dementia Rating (CDR) global score of 0.5 or 1.0.
- A study partner (partner/spouse/carer) consents to the minimum requirements:
  - Study partner will attend at least one screening visit
  - Study partner will be available via phone or in person to provide information to the study as required

Eligible subjects will be randomized in a 1:1 (active:placebo) ratio and return to the study unit on Day 1.

The dosing schedule for subjects is shown in Table 2. The two week initial placebo period will allow for implementation and retraining to assist with dose compliance, without giving participants the intervention drug. The dose level and regime begins at 250 mg a day (Week 3) to monitor for gastrointestinal safety events.

Table 2. Planned Subject Dosing Schedule

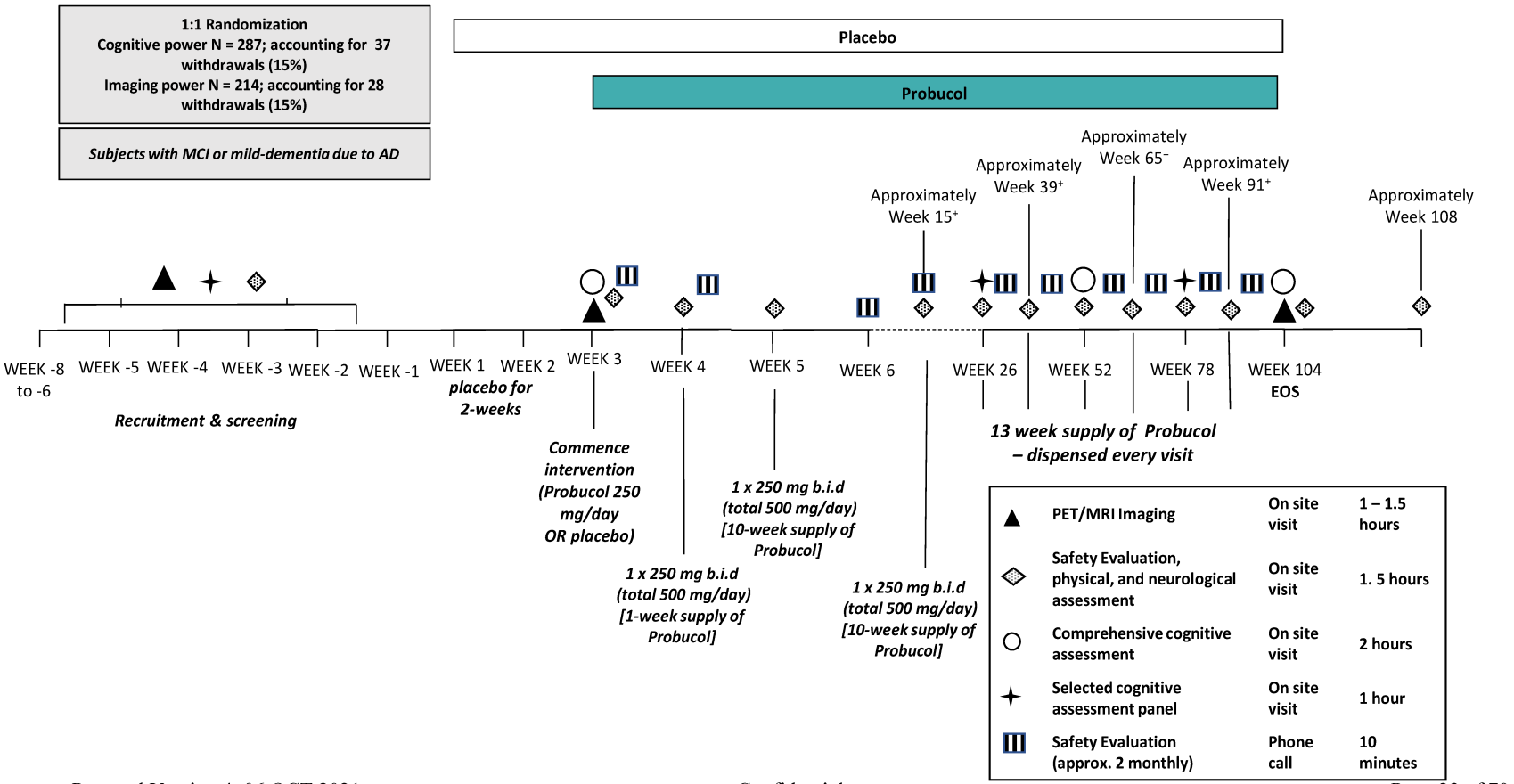
Week	Dose Level	Total Daily Lorelco™ Dose (mg)
Week 1 and 2	1 x placebo taken in the morning, with food.	0 mg
Week 3	1 x 250 mg Lorelco™ (or matching placebo) taken in the morning, with food.	250 mg (or placebo 0 mg)
Week 4 -104	• 1 x 250 mg probucol (or matching placebo) taken in the morning, with food. • 1 x 250 mg probucol (or matching placebo) taken in the evening, with food.	500 mg (or placebo 0 mg)

Subjects will self-administer Lorelco™ or placebo in the clinic under the supervision of site staff on Days 1 (±2 days) on Weeks 1, 2, 3, 4, 5, 15, 26, 39, 52, 65, 78 and 104. All other doses will be self-administered at home, or under the supervision of the designated study partner as appropriate. Lorelco™ and Placebo will be provided in a Webster pack or equivalent to assist with dose compliance.

Patients will also undertake safety and other assessments as required on Days 1 (±2 days) on Weeks 1, 2, 3, 4, 5, 15, 26, 39, 52, 65, 78 and 104.

A study design overview is shown in Figure 1.

Figure 1. Study Design Overview



Patients will be screened between Day -56 to Day -1.

Safety and tolerability assessments will include vital signs, 12-lead ECGs, physical examinations, clinical laboratory tests (haematology, serum chemistry, coagulation, lipid analysis and urinalysis), and AE monitoring, as described in Section 11.8. Blood samples will be collected at specified times, as described in the schedule of assessments (APPENDIX 1).

Efficacy assessments include imaging using, PET scan and Magnetic Resonance Imaging (MRI) as described in Section 11.9. Imaging assessments will be performed at screening, and the 104 week visit or at last study visit if subject discontinues.

A final end of study visit will occur 4 weeks (± 2 weeks) following the last study drug administration.

There are no scheduled overnight confinement periods, however if patients experience any clinically significant adverse events (AEs) during the study, they may be admitted to the clinical facility for further observation at the discretion of the PI.

In the event of strong clinical benefit, and at the discretion of the study doctor, a participant may be reinstated in the study 4 weeks after discontinuation of the participant due to AE. This will be evaluated on a case by case basis.

Regardless of perceived benefit, participants cannot continue probucol at the end of the study as Lorelco™ is not approved for use in Australia. If strong clinical support is identified in the study, this will support effectiveness and phase III trials.

Lorelco™ will be evaluated at a single dose levels with dose increasing to BID by week 4 (Table 2). Thirty patients will initially be enrolled into single-patient cohorts and will be observed during the evaluation period (Week 2 Day 1 to Week 6).

If the patients do not experience any ≥Grade 2 AEs that are deemed related to study treatment, then additional patients may be dosed. The decision to commence dosing in additional patients will be at the discretion of the SRC following review of all AEs, clinical findings, laboratory results.

If in any of the single-patient cohorts a patient experiences a ≥ Grade 2 AE that is not clearly attributed to underlying disease, other medical conditions, or concomitant medications or procedures during the initial safety period, an additional 30 patients will be enrolled at that dose level and evaluated.

6.2 Duration of Therapy and Patient Withdrawal Criteria

In the absence of toxicity or unacceptable adverse events, it is expected that patients will remain on study treatment for 104 weeks. Patients will receive study drug unless they have unacceptable toxicity, withdraw informed consent, or are withdrawn from the study.

Reasons for withdrawal of study therapy regardless of length of time on study include the following:

- Unacceptable toxicity, defined as:
  - Occurrence of an AE that is related to treatment with the study drug which, compromises the patient's ability to continue; or
  - Persistent AE requiring a delay of therapy for more than 4 weeks (28 days).
- Intercurrent illness that requires a delay of therapy for more than 4 weeks (28 days).

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- Patient chooses to withdraw from the study.
- Patient becomes pregnant.
- Patient noncompliance.
- Any other reason, in the opinion of the Investigator, that renders the patient no longer appropriate for study continuation.

Patients will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator, or medically qualified delegate, may discontinue a patient from the study to protect the patient's health.

The date and reasons for withdrawal/discontinuation will be recorded in the electronic case report form (eCRF) and included in the final clinical study report, along with any AEs and necessary medical treatment.

In the event that a patient is discontinued from the study due to an SAE, the Investigator, or medically qualified delegate, will evaluate the urgency of the event. If the situation warrants, the Investigator, or medically qualified delegate, will take appropriate diagnostic and therapeutic measures and make attempts to notify the Sponsor MM. If the situation is not an immediate emergency, the Investigator, or medically qualified delegate, at the clinical study facility will attempt to contact the Sponsor MM for consultation. No medical help, diagnosis, or advice will be withheld from the patient due to an inability to contact the Investigator or medically qualified delegate. The patient will be encouraged to remain available for follow-up medical monitoring. The Sponsor will be notified as soon as possible of any patient withdrawals.

If a participant withdraws consent to participate in this research project, they are entitled to request that all previously retained identifiable biological samples are destroyed, to prevent further analysis according to national provisions.

6.3 Duration of Follow-up

Patients removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE(s). Otherwise, patients will have a final follow-up visit approximately 4 weeks after the last dose of study therapy.

6.4 Suspension or Termination of Study at the Investigational Site

The Sponsor reserves the right to terminate the investigational site or this study at any time. Reasons for termination may include, but are not limited to, the following:

- Unacceptable safety and tolerability of study drug.
- The incidence or severity of AEs or SAEs that are observed in this study indicates a potential health hazard to patients.
- Serious or persistent non-compliance by the Investigator with the protocol, Clinical Trial Research Agreement, principles of the ICH Good Clinical Practice (GCP), or applicable regulatory guidelines in conducting the study.
- Human Research Ethics Committee decision to terminate or suspend approval of the Investigator.
- Investigator request to withdraw from participation.
- Patient enrolment rate is unsatisfactory.

6.5 Duration of the Study

Lam V, *et al. BMJ Open* 2022; 12:e058826. doi: 10.1136/bmjopen-2021-058826

The primary study analysis will occur when target enrolment is complete, and each patient either completes 104 weeks on study, or withdraws. Patients may continue to receive study medication unless evidence of unacceptable toxicities as outlined in Section 6.3.

If a patient is noted to still have ongoing toxicities at the End of Study (EoS) visit, they will be followed until resolution or stabilization of the AE(s).

6.6 Trial stopping criteria

The trial will be discontinued if one or more of these criteria are indicated:

- Substantial deviations from the approved protocol
- Adverse-effects of unexpected type, severity, or frequency are encountered
- As the trial progresses, the continuation of the trial would disadvantage some of the participants as determined by the CI team/researchers, trial monitors or the DSMB.

6.7 Dose Stopping Rules and Individual Dosage Adjustments

Dosing may be stopped or modified if suspected adverse drug reactions, changes in vital signs, ECGs, or clinical laboratory results are observed, and these changes pose a significant health risk. Of particular note for dose discontinuation are the following criteria;

- Corrected QT/QTc interval is in excess of 500 ms, or if it increases > 50 ms compared to baseline (baseline will be calculated as the mean of two time points, screening and baseline day 1).
- Occurrence of QT/QTc interval prolongation in association with symptoms of arrhythmia
- Subsequent prescription of a drug with potential QTc prolongation (Antimalarial; Macrolides; Quinolones; Triazole antifungals; Anti-arrhythmic; Antiemetic; Anti-depressant; Antipsychotics)
- Evidence of Liver dysfunction, or primary biliary cirrhosis
- If for any reason the Investigator determines that continued participation in the trial is not in the participant's best interest.

The study may be terminated at any point in time at the discretion of the Sponsor.

Clinically or medically significant suspected adverse drug reactions, and SAEs considered to be related to study procedures will be followed until resolved or considered stable.

If an unscheduled interruption of treatment occurs, the PI should notify the Sponsor (via the Clinical Research Organization [CRO]) at the earliest possible time. A missed dose will not be made up. In the event that a patient requires an unscheduled interruption of treatment under conditions other than those associated with toxicity, the case will be reviewed by the PI and the MM, and discussed with the Sponsor/CRO to determine whether such a patient will be allowed to resume treatment.

At the discretion of the Investigator, a participant may be reinstated in the study 4 weeks after discontinuation of the participant. This will be evaluated on a case by case basis, and will also be reviewed by the DSMB. Participants will have a safety evaluation 4 weeks following study drug discontinuation.

6.8 Participant Withdrawal

If a participant decides to withdraw from the project, participants are asked to notify a member of the research team. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing with the participant. Participants will be made aware that the decision to withdraw from the study will not affect their future treatment or relationship with the study doctor.

If a participant withdraws consent during the research project, the study doctor and relevant project team members will not collect additional personal information from the participant. However, personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. Participants will be made aware that data collected by the Sponsor up to the time the participant withdraws will form part of the research project results. If a participant decides to leave the research project, they will be encouraged to:

- Tell the study doctor
- Return to the study doctor for one more visit

If a participant withdraws consent to participate in this research project, they are entitled to request that all previously retained identifiable biological samples are destroyed, to prevent further analysis according to national provisions.

If participation in the study is stopped earlier than the 104 weeks indicated, the participant will be required to attend a modified schedule of visits. The participant will visit the study centre 4 weeks after they stop taking the study drug.

6.9 Study Partner Withdrawal

In the event that a study partner withdraws from the study, the study partner will be asked to complete the Study Partner Withdrawal Form and provide a reason for discontinuation. If a study partner withdraws from the study, the participant (or previous study partner) will be asked to nominate a replacement study partner. If a replacement study partner cannot be identified the subject will complete all end of study assessments as deemed appropriate by the Investigator.

6.10 Missed Doses

In the event that a participant misses a dose of the medication, the participant will be instructed that the capsule should be taken as soon as possible. If more than two hours have passed since the scheduled medication time, the participant will be instructed to skip this dose of the medication and resume taking the medication at the next scheduled time. Participants will also be instructed not to double-dose if they miss a scheduled medication. It will be made clear to the participant that taking a double-dose of the medication may increase the risk of adverse side effects.

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7 PATIENT SELECTION

7.1 Number of Patients

Estimated sample sizes are calculated for the two primary outcome measurements: ADAS-Cog and GM atrophy (hippocampal). In order to ensure that the study has sufficient power to detect differences in both of the primary outcomes, the sample size chosen is the maximum of that calculated for each primary outcome.

The primary analysis was an intention-to-treat analysis and included all randomized participants. Data will be analysed using both Generalised Estimating Equations (GEE) and Bayesian Analysis.

The analysis of primary endpoints will use linear mixed-effects models, with random slopes and intercepts. For the ADAS-Cog, using mixed model analysis published estimates from the ADNI cohort17 suggest a sample size of 125 AD participants per trial arm (total N = 250) will be required for power at 0.8 to detect a drug effect of 25% over two years and assuming a decline from baseline of 1.10 standardised units on the composite (SD change = 0.83).

For the MRI markers, Ledig et al. (2018)[24] reported the sample sizes required for a 25% intervention reduction over two years based on 322 patients with AD (with 117 followed for 24 months) and a reduction of 10.2% (6.2) for hippocampus18. Sample size calculations based on hippocampal volume suggest that 93 subjects per treatment arm are required (total N = 186).

Assuming a 20% attrition rate, a sample of 314 subjects will be recruited for the Cognitive study, and 233 subjects will be randomly chosen for the Imaging study.

7.2 Inclusion Criteria

Patients must satisfy all of the following criteria to be enrolled in the study:

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:
    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 less OR free recall score ≤17
    d. 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) ≤ 450 msec for males and ≤ 460 msec for females at screening and on Day 1, prior to dose administration *(the mean of two measurements will be used to determine eligibility)*.
6. Evidence of adequate hepatic function at screening, as defined by the following:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit

of normal (ULN) (≤5 × ULN if liver metastases are present); and

b. Total bilirubin ≤1.5 × ULN (< 2.0 x ULN for subjects with liver metastases or documented Gilbert's syndrome).

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 x the upper limit of normal for the local laboratory reference range at the screening visit.
10. FBC must be within < 1.5 x the upper limit of normal for the local laboratory reference range at the screening visit.
11. Female volunteers:
    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, or
    b. 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 (refer to Appendix 5) from the time of signing the consent form until at least 30 days after the last dose of the study drug.
12. Male volunteers:
    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.
13. Estimated life expectancy of at least 2 years, in the opinion of the Investigator.
14. Have suitable venous access for blood sampling.
15. Be willing and able to comply with all study assessments and adhere to the protocol schedule and restrictions.
16. A study partner (partner/spouse/carer) consents to the minimum requirements:
    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.

7.3 Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for inclusion

in the study:

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:
    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. Unstable atrial fibrillation including paroxysmal atrial fibrillation. Medicated, stable atrial fibrillation will be assessed by the study doctor on a case-by-case basis
    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 Leracol™ and for the duration of the study . These include (but are not limited to):
    a. *Medications:* See APPENDIX 7.
    b. With significant central anticholinergic effects,
    c. Sedatives,
    d. Antiparkinsonian medications that cannot be stopped prior to study entry,
    e. Any investigational treatment for AD
    f. *Foods:* Grapefruit or Seville orange (or grapefruit- or Seville orange-containing products, including juices).
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. 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;
    - Specifically contraindicated with Probucol, 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 active human immunodeficiency virus (HIV-1 or HIV-2), hepatitis B or hepatitis C virus (HCV) at the Screening visit.
18. Any inflammatory or chronic pain condition that necessitates regular use of opiates/opioids,.
19. Major surgery within 28 days of Day 1 Week 0, or minor surgical procedures within 7 days of Day 1 Week 0.
20. For women of childbearing potential, a pregnancy hCG test > 5 U/L 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.

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

8 INVESTIGATIONAL PRODUCT

8.1 Study Drug Supply

8.1.1 Lorelco™

Lorelco™ tablets will be supplied by a designated manufacturer/distributor of the Sponsor. The Sponsor will provide the site pharmacy with a sufficient quantity of Lorelco™ for the conduct of the study. The Lorelco™ tablets will be over-encapsulated inside an opaque capsule shell and backfilled with Microcrystalline cellulose. Individual doses of Lorelco™ to be administered in the study will be dispensed by the site pharmacy.

Detailed product information (including storage details) is provided in the Investigator's Brochure.

8.1.2 Placebo

Matching placebo opaque capsules with no active ingredients and a filler of microcrystalline cellulose will be compounded by Oxford Compounding to ensure they are identical in nature. Microcrystalline cellulose was chosen for use in the placebo because it is an inert, insoluble fibre that is not absorbed into the systemic circulation

8.2 Identification and Description of Lorelco(TM)

The probucol used in this study will be commercially available tablets (Lorelco™ white to slightly yellowish white tablet, diameter 11.1 mm, thickness 4.5 mm) produced by Aventis Pharmaceuticals and wholesaled by Otsuka Pharmaceutical Co., Ltd. for the strength of 250 mg. Oxford Compounding Pharmacy Pty. Ltd. will secure Lorelco™ 250 mg tablets on behalf of the trial sponsor and will be responsible for over-encapsulation, bottling and dispensing of coded batches to the host sites. Matching placebo capsules with no active ingredients and a filler of microcrystalline cellulose will be compounded by Oxford Compounding to ensure they are identical in nature. Microcrystalline cellulose was chosen for use in the placebo because it is an inert, insoluble fibre that is not absorbed into the systemic circulation.

8.3 Stability of Lorelco™

Lorelco™ capsules (250 mg) are to be stored at room temperature in sealed conditions. Current stability data indicates that the capsules are stable when stored as described for up to 36 months.

8.4 Lorelco™ Study Drug Packaging and Labelling

Lorelco™ 250 mg capsules will be provided to sites in Webster packs from Oxford Compounding.

The label will include the following information. The clinical trial material will be clearly marked according to national requirements regarding use for clinical trial investigation only and will be labelled with the drug name, study reference number, and storage conditions.

It will be the responsibility of the investigator to ensure that accurate accountability records are maintained throughout the study. The pharmacy will prepare and dispense the

investigational product according to the randomization scheme.

Individual dosing containers will be labelled by the investigational site with the following:

- "For Clinical Trials Use Only"
- Protocol Number
- Principal Investigator Name
- Subject name and subject number/ Randomization No.
- Dosing directions
- Name of Sponsor and Contact Details
- Batch Number
- Expiry Date
- Storage Conditions
- Keep in a cool, dark place (avoid light exposure)
- Keep out of reach of children

All investigational products will be packaged and labelled. Labelling of the investigational products will be performed in accordance with Annex 13 of the Good Manufacturing Practices for investigational products labelling requirements.

Detailed instructions for the preparation labelling and supply of Lorelco™ capsules are described in the study Pharmacy Manual.

8.5 Handling and Storage

Study drug supplies will be stored securely at the site and/or designated Pharmacy according to the State and Commonwealth Laws.

The site Pharmacy must ensure that deliveries of study drug are correctly received by a responsible person, that all receipts of drug shipments are recorded on the appropriate Drug Accountability forms prepared by the site Pharmacy and that all study drugs are stored in a secure area under recommended storage conditions, as listed in this protocol (or the CMI/product information sheet. It is also the responsibility of the PI to ensure that the integrity of packaged study drug not be jeopardised prior to dispensing. Only patients enrolled in the study may receive the study drug(s), in accordance with all applicable regulatory requirements. Only authorised and trained site staff may supply or administer the study drug.

At the scheduled study visits where the patient will consume the study drug at the study site, individual doses will be dispensed by the site Pharmacy staff member on the morning of dosing and recorded in the drug accountability records. Patients will also be provided with appropriate quantity of Lorelco™ for at-home dosing (per the Schedule of Assessments) and will be instructed by study staff on the handling and storage of the study drug(s). The study Pharmacy Manual will define the procedures for dispensing.

8.6 Accountability of Study Drug Supplies

All material supplied is for use only in this study and should not be used for any other purpose.

The PI is responsible for study drug accountability, reconciliation and record maintenance at the study site. In accordance with all applicable regulatory requirements, the PI or designated trained site staff must maintain study drug accountability records throughout the course of the

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study. This person will document the amount of Investigational Product received by the site Pharmacy and the amount supplied and/or administered to and returned by patients, if applicable. Used containers of study drug will be retained and sequestered per patient and made available to the study monitor during study drug reconciliation.

The date and time of dose preparation and release will be maintained to support administration of the study drug within the predefined use period. The shipment/receipt/supply records as well as records of dispensing and administration will be verified by a second member of staff. The site Pharmacy will dispense the study drugs to the study site and the study site staff will administer the study medication only to patients included in this study following the procedures set out in the study Pharmacy Manual and in this protocol. Dispensing and supply/administration will be verified by a second staff member. Each patient will be given only the study drug preparation carrying his/her study number. Study drug administration will be documented in the eCRF and other study drug record(s). The PI (or designated trained site staff) is responsible for assuring the retrieval of all left-over study supplies following administration to patients.

The inventory must be available for inspection during the study. When requested in writing by the Sponsor and following drug accountability and reconciliation, unused study drug supplies may be returned to the Sponsor or destroyed by the PI (or delegate), provided destruction does not expose humans to risks from the study drugs. Records shall be maintained of the return or destruction of the study drug. These records must show the identification and quantity of each unit returned or disposed of, the method of destruction (taking into account the requirements of local law), and the person who returned or disposed of the study drug materials. Such records must be submitted to the Sponsor.

Lam V, *et al. BMJ Open* 2022; 12:e058826. doi: 10.1136/bmjopen-2021-058826

9 ADMINISTRATION OF INVESTIGATIONAL PRODUCTS

9.1 Administration of Investigational Products

Delegated study site personnel will supervise and instruct patients on the administration of the Investigational Products.

9.1.1 Investigational Product Administration

The dose and number of 250 mg Lorelco™ or placebo capsules will be administered as described in Table 2. Patients will self-administer investigational product (under the supervision of site staff, or at home) orally, with a full cup (approximately 240 mL) of noncarbonated room temperature water.

Dosing instructions will be detailed in the study Pharmacy Manual and will be provided to the patients at each Investigational Product dispensing.

Orally administered Investigational Products must be swallowed whole and not chewed, divided, dissolved or crushed.

For all drug administrations performed during "at home" periods, participants will self-dose at home unsupervised. Patients will be instructed to return all Webster packs to site staff at each clinic visit for accountability checks. Patients will be instructed not to take the Lorelco™ on clinic visit days until the safety blood samples have been taken.

10 CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

Compliance to these restrictions will be assessed prior to first dosing and throughout the duration of the study.

10.1 Concomitant Medications

In general, all supportive measures consistent with optimal patient care will be given throughout the trial. However, the following restrictions apply:

- Any prescription or non-prescription medications that are strong QTcF prolongation inducers (APPENDIX 7) are prohibited within 7 days prior to the first dose administration of Lorelco™ and throughout the study;
- Any prescription and non-prescription medications, herbal remedies, vitamins and nutritional supplements taken by patients must be reviewed and approved by the Investigator.

All concomitant therapies should be recorded in the patient's source documents and corresponding eCRF at each scheduled visit. All medication changes since the last visit will be captured, including new medications, changes in dose or schedule for existing medications, and cessation of medications. For new medications, the dose, route of administration, schedule and indication will be recorded. Dates of changes to medications (commencement, cessation and/or alteration in dose or schedule) will also be captured.

Where possible, any concomitant therapy should be withheld until at least 1 hour following study drug administration on each day.

10.2 Fasting Requirements

Patients will be required to fast for a minimum of 8 hours prior to collection of the safety laboratory blood samples at each visit.

10.3 Supportive Care

The use of supportive care including steroids and antibiotics, will be permitted as clinically indicated and according to institutional guidelines.

Surgeries must be discussed with the Sponsor MM and Investigator prior to determining if patients can remain on study.

10.4 Contraception

Female patients of child-bearing potential, with a fertile male sexual partner, should use highly effective methods of birth control (APPENDIX 6) from signing the consent form until at least 3 months following the last dose of study therapy.

Male patients, who are not surgically or biologically sterile, should use a condom in addition to having the female partner a use highly effective methods of birth control (APPENDIX 6) from signing the consent form until 3 months following the last dose of study therapy.

All study patients must be willing to ensure that corresponding sexual partners practice these same methods of highly effective birth control for the same duration.

11 STUDY PROCEDURES

For the exact timing of each procedure, please refer to the Schedule of Assessments (SoA) in APPENDIX 1. Clinical staff are required to perform assessments at the nominated timepoints within the time windows indicated in SoA. Actual times of procedures for each patient may vary depending on scheduling and will be recorded in the eCRF. In the event of multiple procedures scheduled at the same time, the order, where possible, will be (1) vital signs, (2) 12-lead ECG, (3) safety laboratory blood sampling.

11.1 Informed Consent

The Information and Informed Consent Form (ICF) will be provided to patients at Screening and signed prior to any study procedures being performed. Investigators at each site are responsible for maintaining a record of all patients screened, including both those who enter the study and those who do not.

11.2 Medical History

A full medical history will be obtained at Screening, including a detailed neurologic history, other medical and surgical history, medication history and drug allergies. Demographic data including gender, ethnicity, and race will be recorded.

11.3 Height and Weight

Body height (centimetres) and weight (kilograms) will be measured, and body mass index (BMI) will be calculated. Height should be measured on a wall-mounted stadiometer. Weight should be measured in light-weight clothing, without shoes.

11.4 Pregnancy Test

Female patients (women of child-bearing potential (WOCBP) only) will complete a blood chorionic gonadotropin (hCG) pregnancy test at Screening, Baseline, and again at their EoS visit. A hCG pregnancy test will be conducted at other designated time points as per the SoA. If any of the hCG tests are > 5 U/L but < 25 U/L, a second hCG test will be completed in 7 days. In instances of a positive pregnancy result at any time points, the patient will be withdrawn from the study. Patients withdrawn from the study due to pregnancy may be replaced at the discretion of the PI.

11.5 Safety and Tolerability Assessments

Safety will be determined by evaluating physical and neurological examinations, vital signs, clinical laboratory parameters, 12-lead ECGs and AEs. If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator (or delegate). The timing of all safety assessments is presented in the SoA. Clinical staff are required to perform the assessments at the nominated time-points within the time windows indicated in the SoA, and as indicated below.

Abnormal vital signs assessments, clinical laboratory safety tests, ECGs and physical examinations that are judged by the PI as clinically significant will be recorded as AEs or SAEs. Clinically significant findings that are assessed by the Investigator to be likely due to the normal disease course in a patient should not be listed as an AE, however, should be reported as a clinically significant finding.

11.5.1 Vital Signs

Vital signs assessments will include systolic and diastolic blood pressure, heart rate (HR), respiratory rate (RR) and body temperature (tympanic temperature is acceptable). Patients should be resting in a supine position for at least 5 minutes prior to and during vital signs measurements.

11.5.2 Clinical Laboratory Safety Tests

Tests performed by the local laboratory are described in APPENDIX 5. Tests for any out of range results may be repeated following PI (or delegated medical officer) review. Out of range results obtained at screening may be repeated once at any time during the screening window up to (and including) Day -1, at the discretion of the PI.

All safety laboratory assessments will be assessed by a certified local laboratory, using that laboratory's normal ranges. The Investigator must review the laboratory report and document this review.

Fasting Safety Laboratory Blood Tests

Participants will be required to fast for a minimum of 8 hours prior to collection of this sample. Water is permitted.

Haematology and Serum Chemistry

Blood samples for haematology, serum biochemistry (including liver function tests) will be collected at selected time points throughout the study as defined in the SoA. Test results will be monitored for potential AEs, including gastrointestinal bleeding (haemoglobin) and rhabdomyolysis (plasma CK).

11.5.3 Electrocardiogram

Twelve-lead ECGs will be assessed (including but not limited to the measurements of ventricular HR, PR interval, RR interval, QRS duration, QT interval and QTcF). Screening and prior to first dose, triplicate 12-lead ECGs (collected within 5 minutes with each reading separated by at least 1 minute) will be taken to establish eligibility at baseline. Triplicate ECGs will also be recorded at the EOT visit. The average value for the triplicate will be utilised for assessing QTcF inclusion criteria. All other ECGs will be single readings. However, if any of the ECG measurements is out of normal range, it will be repeated in triplicate (within 5 minutes, with each reading separated by at least 1 minute).

ECG normal ranges are as follows:

- PR interval: 120 msec – 220 msec (inclusive);
- QRS duration: < 120 msec;
- QTcF ≤450 msec (males); QTcF ≤460 msec (females);
- HR 45-100 beats/min (inclusive)

If the "re-check" triplicate's average is still above these parameters, the PI shall be notified for a determination on further action. The same model of ECG machine should be used for Screening, pre-dose and post-dose readings for all patients. ECGs will be taken after at least 5 minutes in a supine quiet rest. ECGs will be interpreted, signed and dated by the PI, or medically qualified designee. The ECGs will be classified as normal, not having a clinically significant abnormality or having a clinically significant abnormality. In addition, ECG

parameters of HR, PR interval, QT interval, PR interval, R-R interval, QRS duration, and QTcF will be noted on the eCRF.

11.5.4 Physical Examination

A full physical examination will be performed at Screening and at the EoS visit. The full physical examination will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, lymph nodes, heart, chest, abdomen and extremities, and a neurological examination (assessment of speech, cranial nerves, peripheral nerves, motor power, deep tendon reflexes, sensation, coordination and gait) and any other focussed assessments suggested by the presence of specific symptoms. All other scheduled assessments will be symptom-directed.

All physical examinations are to be conducted by a medically qualified Investigator.

11.6 Efficacy Assessments

11.6.1 Screening Assessments

Free and Cued Selective Reminding Test (FCSRT)[14]: The FCSRT assessment will be performed at screening only for eligibility determination. A cueing index of ≤ 0.79 or free recall score of ≤ 17 is required for study entry. The FCSRT is a cued recall test that utilises a controlled encoding technique to ascertainthat impairment in recall and cueing are due to a memory deficit rather than a failure of encoding. Memory impairments due to AD are hippocampal dependent and believed to be characterized by a deficit in recall, often not recovered by cueing. The cueing index measuresthe ability a participant may benefit from being reminded of specific cue words to recall the target word.

Clinical dementia rating scale (CDR)[15]: The CDR provides two scores, a global score (GS) and a sum of boxes (SOB). The GS distinguishes a participant's level of impairment into the following categories: 0 (normal); 0.5 (questionable dementia; 1 (mild dementia); 2 (moderate dementia) and 3 (severe dementia). The SOB is scored from 0 – 18 with higher scores indicating a greater level of impairment. The scale covers six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Information to evaluate each rating is obtained through a semi-structured interview with initially the study partner, followed by the participant and takes approximately 40 – 60 minutesat screening.

Mini Mental State Examination (MMSE)[16]: The MMSE is a brief, widely used 30-item assessment of global cognition examining orientation, registration, calculation, recall, attention and language. WORLD backwards will not be used in this protocol. Participants who score <22 at screening will be ineligible for study entry. MMSE will be assessed at screening and EoT (104 weeks).

11.6.2 Primary Cognitive Assessment

Alzheimer's Disease Assessment Scales-Cognitive Subscale test (ADAS-Cog)[17]: The Alzheimer's Disease Assessment Scale-Cognitive Subscale test (ADAS-Cog) is the most widely used test to measure cognition in RCT's for AD. Taking 30 to 40 minutes to administer it is commonly used in clinical trials as it can determine incremental improvements, or decline

in cognitive functioning. The ADAS-Cog12 version consists of the following tasks: Word Recall Task; Following Commands; Constructional Praxis; Delayed Word Recall; Naming Objects and Fingers; Ideational Praxis; Orientation; Word Recognition; Spoken Language; Comprehension and Word Finding Difficulty. Inclusion of the delayed word recall component has shown an increased ability to detect change in the MCI population. Sensitivity of ADAS-Cog is indicated by a scoring differential of approximately six-fold in patients with the earliest manifestation of AD compared to aged-matched health controls. The full suite of ADAS-Cog will be at baseline, 26, 52, 78 and 104 weeks.

11.6.3 Secondary Cognitive Assessment

Alzheimer's Disease Co-operative Study Mild Cognitive Impairment Activities of Daily Living (ADCS-MCI-ADL24)[18]: The ADCS-MCI-ADL24 is a study partner 24-item questionnaire evaluating perceived difficulties with functioning in several activities of daily living across the a variety of domains. The MCI version of the original ADCS-ADL is more sensitive to minor deficits that may be present and provides an overall impairment score, with a higher score indicating a higher level of functioning.

Depression Anxiety Stress Scale (DASS-21)[19]: The DASS-21 is a self-report 21-item measure to determine levels of depression, anxiety and stress. It is a shorter version of the original 42-item questionnaire, containing seven questions for each of the domains. Participants are read a statement and asked to rate each statement on a four-point scale as to how much it relates to them. These scores are tallied for each domain and multiplied by two to give a total for depression, anxiety and stress to determine psychological well-being in comparison to normative values. DASS-21 will be administered at day 1/week 1, weeks 26 and 104 (EoS).

11.7 Secondary *in vivo* Imaging Outcomes

Amyloid imaging will be done with amyloid tracer PET scans at baseline and at 104 weeks. Dynamic and static PET imaging will be acquired. Analysis will include i) visual assessment of amyloid load ii) quantitative assessment of amyloid burden, including standard uptake value ratio (SUVr) iii) dynamic imaging for blood perfusion measures. The protocol for imaging will be standardised for the baseline and follow-up scans. Participating PET sites will undertake camera calibration prior to study entry (facilitated by ARTnet Australasian Radiopharmaceutical Trials Network).

The MRI protocol will include the acquisition of 3 sets of data [1] Volumetric isotropic T1 scan (6.5 min). This will allow voxel wise segmentation and volumetric analyses (e.g. GM volume) to assess volume changes in characteristic locations which can yield diagnostic accuracy on approximately 90%[14]. Mesial temporal lobe (hippocampus and entorhinal cortex via Scheltens grading), global cortical atrophy (Pasquier scale) and parietal atrophy (Koedam score) as well as inferior lateral ventricle size will be assessed. Brain volume indices indicate that patients with AD have accelerated rates of brain volume loss of up to 4.5% per year compared to normal controls (1%). [2] 3D FLAIR scan (3.5min). This will demonstrate the small vessel ischaemic lesion load which will be scored according to the Fazekas method[15]. [3] Susceptibility weighted imaging (SWI) – a means of measuring micro bleed load and indicator of amyloid angiopathy and for the purposes of Quantitative Susceptibility Mapping (QSM) (~7 mins)[15]. This method quantitates regional brain iron content which is altered in AD compared with normal controls. Mesial temporal, basal ganglia, cingulate, cortical region

of interest comparisons will be performed at baseline and at treatment completion. Visible micro bleeds will be graded using the Brain Observer Micro-Bleed Scale (BOMBS).

11.8 Laboratory evaluations

Blood samples will be utilised to monitor general wellbeing such as liver function; lipid profiling; and C-Reactive Protein (CRP). Blood samples will be collected by venepuncture at screening, baseline, weeks 3, 4, 5, 15, 26, 39, 52, 65, 78, 91 and 104 weeks (an estimated 13 mL of blood will be collected per visit and a total of 160 mL will be collected over the 2-year study). During each visit (screening, baseline, weeks 3, 4, 5, 15, 26, 39, 52, 65, 78, 91, 104 and 4 weeks following completion of the study), vital signs (blood pressure, heart rate, respiratory rate and body temperature) and electrocardiogram (ECG) results will be recorded. All ECGs will be completed by the study doctor or clinical nurse. All ECGs and safety data will be assessed by the study doctor.

11.9 APOE

Apolipoprotein E will be collected to determine APOE genotype, with particular interest in identifying individuals with APOE4 allele (associated with increased risk of AD). Approximately 3 mL of blood will be collected at screening for APOE analysis.

11.10 Total Blood Sample Volumes

Blood samples for clinical safety laboratory tests, pregnancy tests will be collected from each patient throughout the study, resulting in the following approximate blood volumes per patient for Screening, each completed cycle of treatment and the EoS visit. Additional blood samples may be required from any of the study patients if required for safety reasons.

Table 3. Approximate Blood Sample Volumes to be Collected per Patient

Sample Type		***Blood volume per participant (mL)***	
	Screening	**Visit[c]**	**EoS**
Clinical laboratory (Safety) tests (haematology) [a]	4 mL (1 x 4 mL)	40 mL (10 x 4 mL)	4 mL (1 x 4 mL)
Clinical laboratory (Safety) tests (serum biochemistry) [a, b]	9 mL (1 x 9 mL)	90 mL (10 x 9 mL)	9 mL (1 x 9 mL)
APOE sample	3 mL (1 x 3 mL)	-	-
Total Blood Volume	**16 mL**	**130 mL**	**13 mL**

[a] Also includes fasting safety laboratory blood samples, where required.
[b] Also includes serum pregnancy and FSH testing, where required.
[c] visits occur at week 3, 4, 5, 15, 26, 39, 52, 65, 78, 91

12 ASSESSMENT AND MANAGEMENT OF ADVERSE EVENTS

12.1 Adverse Event Definitions

An **AE** is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not considered related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

Any AE where a causal relationship with the investigational product is at least a reasonable possibility (possibly/probably or definitely related), is referred to as an **Adverse Drug Reaction**.

An **SAE** is any AE that, at any dose:

- Results in death;
- Is life-threatening (The term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe);
- Requires inpatient hospitalization or prolongation of an existing hospitalization (only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations);
- Results in persistent or significant disability/incapacity (an AE that results in a substantial disruption of a person's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect (A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the study drug);

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is any AE:

- That is serious
- Where there is a least a reasonable possibility of a causal relationship between the event and the study drug
- That is considered unexpected (i.e., the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed). For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure

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listed only cerebral vascular accidents. "Unexpected" as used in this definition, also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Abnormal laboratory findings (e.g., serum chemistry, haematology, coagulation and urinalysis) **or other abnormal assessments** (e.g., ECGs, vital signs) that are judged by the PI as clinically significant will be recorded as AEs or SAEs if they meet the definitions stated above. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The PI will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Assessments may be repeated once, if abnormal values were recorded in the first instance, at the discretion of the PI. Any clinically significant laboratory finding that is assessed by the Investigator to be likely due to the normal disease course in a patient should not be listed as an AE, however, should be reported as a clinically significant laboratory finding.

12.2 Evaluating AEs and SAEs

12.2.1 Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each AE and SAE will be graded using the most current version of the Common NCI-CTCAE v5.0 (or higher) five-point scale:

- **Mild (Grade I)**: Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated;
- **Moderate (Grade II)**: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL);
- **Severe (Grade III)**: Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL;
- **Life-threatening (Grade IV)**: Life-threatening consequences; urgent intervention indicated;
- **Death (Grade V)**: Death related to AE.

If an AE has multiple aspects, the aspect with the highest severity will be graded.

The term severe is a measure of severity. Thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

12.2.2 Assessment of Causality

The Investigator will make an assessment as to the relationship between the investigational product and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine whether or not the AE/SAE is causally related to the study drug. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and

Lam V, *et al. BMJ Open* 2022; 12:e058826. doi: 10.1136/bmjopen-2021-058826

investigated. The Investigator will also consult the Investigator's Brochure (for Lorelco™) including the CMI/product information in the determination of his/her assessment.

The causal relationship of the study drug to an AE will be rated according to the following 5-point scale:

- **Unrelated:** Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable;
- **Unlikely:** Does not follow a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered;
- **Possibly:** Follows a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered;
- **Probably:** Clear temporal association with improvement on cessation of study drug or reduction in dose. Reappears upon re-challenge or follows a known pattern of response to the study drug;
- **Definitely:** An AE that cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

There may be situations when 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 prior to transmission of the SAE form to the Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE form and the eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

12.2.3 Action Taken and Outcome

For all AEs reported the actions taken and outcomes will be specified.

Actions taken may include any of the following:

Action(s) taken with study drug:

- Dose not changed
- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not applicable
- Unknown

Other action(s) taken:

- No action
- Medication required
- Termination of a concomitant medication
- Change of the dose of a concomitant medication
- Hospitalization or prolongation of hospitalization (please complete SAE-Form)

- Initiation/termination of a non-drug therapy
- Other (please specify).

The following terms and definitions are used in assessing the final outcome of an AE:

- **Recovered** - The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent.
- **Recovering** - The condition is improving and the patient is expected to recover from the event.
- **Recovered with sequelae** - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered** - The condition of the patient has not improved, and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- **Fatal** - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as “recovered”, “recovering”, “recovered with sequelae” or “not recovered”. An AE with fatal outcome must be reported as an SAE.
- **Unknown** - This term is only applicable if the patient is lost to follow-up.

12.3 Procedures and Time Period for Detecting Adverse Events

The Investigator (or designee) is responsible for detection, recording and reporting of events that meet the criteria and definition of AEs.

As a consistent method of soliciting AEs, the participant shall be asked a non-leading question such as: "How do you feel?”.

Detection and recording of study related AEs and SAEs extends from the signing of the consent form until completion of the last study related procedure (including follow-up for safety assessments).

Any AE reported or observed after the start of dosing with any study treatment until completion of the last study related procedure (includes follow-up for safety assessments) will be recorded as a treatment-emergent AE.

Any change in health status that is reported or observed after informed consent but prior to starting study treatment and is deemed by the study Investigator to be “not related” to study procedures, will be documented as medical history.

Any pre-existing conditions or signs and/or symptoms present in a patient prior to any involvement in the study (i.e., before informed consent) should be recorded as medical history. In addition, any change in health status, which is reported after informed consent but started prior to informed consent by the volunteer, will be documented as medical history.

Any worsening of a pre-existing condition that occurs following informed consent will be recorded as an AE.

A post-study AE/SAE is defined as any event that occurs outside of the nominal AE/SAE study detection period. Investigators are not obligated to actively seek AEs/SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has completed the study and he/she considers the event reasonably

related to the study treatment, the Investigator will promptly notify the Sponsor.

Patients must be provided with an "Emergency Wallet Card" indicating the name of the study treatment, the study number, the Investigator's name, and emergency contact number.

12.4 Recording of AEs and SAEs

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the eCRF and/or other sources. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion may be reported as "upper respiratory infection"). Investigators must record in the eCRF the date of onset of the event, their opinion concerning the relationship of the AE to study therapy. Severity of the event, whether the event is serious or nonserious, actions taken to manage the event, the outcome of the event, and date of resolution where applicable.

Any change to the severity of an AE must be recorded as a separate AE, ensuring that the end date and time of the preceding AE matches the start date and time of the subsequent AE, so that the overall duration of the AE is continuous.

12.5 Reporting of SAEs and SUSARs

In accordance with ICH guidelines for GCP, a copy of the written report of any SAEs should promptly be sent to the study Sponsor. The Investigator must notify the study Sponsor (or the Sponsor designated study Safety Officer) within 24 hours of becoming aware of the occurrence of an SAE.

Information regarding SAEs will be transmitted to the Sponsor (or the designated study safety officer) using an SAE Form as described in the study Safety Reporting Plan. The SAE Form must be completed and signed by a member of the Investigational staff and transmitted to the Sponsor (or the designated study Safety Officer) within 24 hours (Table 9). Any new or updated clinical information on the SAE will be recorded on a new SAE form and sent to the Sponsor designated study Safety Officer within 24 hours of the information being available. The initial and follow-up reports of an SAE should be made by e-mail.

Table 4. Contact details for transmission of SAE reporting forms to the Sponsor designated Safety Officer.

Sponsor designated safety officer details for SAE reporting	Name: Emily Corti Phone: +61 431 584 166 Email: emily.corti@curtin.edu.au

The Investigator must report SAEs to the appropriate Human Research Ethics Committee that approved the protocol unless otherwise required and documented by the Ethics Committee.

It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR. The Investigator's opinion regarding the assessment of expectedness (if provided) and causality will be taken into account in the Sponsor's determination of the SAE as a SUSAR. The causality assessment given by the Investigator cannot be downgraded by the Sponsor.

SAEs (and SUSARs) will be reported to competent authorities in accordance with national

requirements. The Sponsor assumes responsibility for appropriate reporting of SAEs (and SUSARs) to the regulatory authorities.

12.6 Follow-up of AE and SAE

After the initial AE/SAE report, the Investigator is required to proactively follow each patient and provide further information to the Sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. Adverse events and SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves;
- The event stabilizes;
- The event returns to Baseline, if a Baseline value is available;
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct;
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

The Investigator will ensure that AE/SAE follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE/SAE. If a participant dies during participation in the study or during a recognised follow-up period, where possible, the Sponsor will be provided with a copy of any post-mortem findings, including histopathology.

Due to the coronavirus SARS-COV-2 (COVID-19) pandemic, Investigators must also ensure compliance with local governing legislation and reporting requirements associated with COVID-19 infections.

12.7 Exposure *In Utero* Management and Reporting

In instances of pregnancies or suspected pregnancies (including a hCG pregnancy test > 25 U/L regardless of age) while a patient is on study treatment, dosing of Lorelco ™ (and placebo) must be discontinued immediately. Pregnant patients (or pregnant partners of male patients) should be advised to call their healthcare provider.

The Investigator will notify the Sponsor and designated study Safety Officer of any pregnancy and document the pregnancy on the Exposure in Utero Form as described in the study Safety Reporting Plan.

The Investigator shall obtain informed consent from a pregnant patient (or a pregnant female partner of a male patient) to allow the Investigator (or delegate) to conduct follow-up throughout the gestational period and on the infant following delivery. The Investigator shall follow-up newborn infants that have been exposed to study drug *in utero* for a minimum of 12 months. Upon discovery of any congenital anomalies (or neonatal deaths) the Investigator

shall submit a follow-up report to the Sponsor (or designated study Safety Officer) using an SAE Form (as per the study Safety Reporting Plan) including information regarding the status of the newborn. A miscarriage or abortion shall also be reported by the Investigator to the Sponsor (or the designated study Safety Officer) using an SAE Form.

12.8 Data Safety Review Committee

A Data Safety Monitoring Board (DSMB), comprised of external parties, has been established for the PIA-Study. Indicated are experienced clinical researchers in geriatric medicine; cardiology and electrophysiology; lipid, stroke and general medicine; cardiovascular medicine and clinical trials; and in data management. The DSMB will initially meet on a quarterly basis (twice) followed by 6-monthly meetings unless deemed required more often. Additional meetings will be held as required on ad hoc basis. To address the risk of QT/QTc prolongation, ECG safety monitoring will be completed and read on site by the study doctor during screening and study visits at baseline and weeks 3, 4, 5, 15, 26, 39, 52, 65, 78, 91, 104, and 4 weeks following completion of the study. Measurement of QT/QTc interval will be completed using automatic algorithms and manual measurement (to the nearest 5 milliseconds and referencing to normal values)[20]. In the event of a severe adverse effect, such as prolonged QT interval, blinded high quality ECG data will be made available for review by the DSMB. In addition, ECG data will be reviewed by the DSMB 3 monthly (initially) and will be blinded to time, treatment, and subject identifier. Correction of QT interval will be determined using Fridericia's correction: QTcF=QT/RR1/3. Absolute QTc interval prolongation (> 500 ms) and change from baseline in QTc interval (> 50ms) will also be used in consideration for discontinuation or change in treatment protocol. As heart rate can influence corrected QT interval (potential for both over, or under-correction), it is important to ensure that the participant is at rest before and during the ECG. The study doctor will ensure a short rest period prior to administering the ECG to ensure altered heart rate is not a potential confounding factor in QT interval analysis. Furthermore, to ensure interpretation of QT/QTc interval data is correct, the QT/QTc interval data will be analysed using both analyses of central tendency (e.g., means, medians) and categorical analyses (e.g., absolute QTc interval prolongation, change from baseline in QTc interval). If a participant is prescribed a second or subsequent drug with potential QTc prolongation while taking probucol, additional ECGs will be completed to monitor the risk of QTc prolongation. In the event of a severe adverse event, or if prolonged QT/QTc interval continues following discontinuation of Lorelco™, participants may be referred to a cardiologist.

Furthermore Professor Rukshen Weerasooriya (Clinical Professor of Medicine, University of Western Australia and Hollywood Hospital, Western Australia), a leading expert in managing patients with cardiac arrhythmia's will serve as an Associate Investigator for this study and will ensure the study doctor is trained and quality assured in assessing QT/QTc interval, and will review eligibility for participation and safety reports when required.

Participants will be provided with a list of potential side effects of the treatment medication and will be advised to contact the study doctor should any side effects occur. Participants will also be instructed to call 000 should they experience an allergic reaction to the treatment drug. Additionally, participants will be advised to seek immediate medical attention if symptoms such as light-headedness, dizziness, palpitations, shortness of breath, or fainting occurs. The study doctor will also phone participants at week 3, 4, 6, 20, 29, 47, 55, 73 and

81 to discuss if the participant has experienced any side effects. If side effects are noted by the participant, continuation of the study will be determined on a case by case basis by the study doctor. Participants will also be required to attend safety evaluation appointments at approximately week 3, 4, 5, 15, 26, 39, 52, 65, 78, 91, 104 and approximately 4 weeks following the end of the study. These sessions will be to monitor potential side effects and/or adverse events.

13 STATISTICS AND DATA ANALYSIS

Detailed methodology for summaries and statistical analyses of the data collected will be documented in a separate Statistical Analysis Plan (SAP) that will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the Clinical Study Report (CSR).

This section describes the general framework to be used for the analysis and presentation of data in this study. The information described in this section may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data that could affect planned analyses. All available data will be included in data listings. Data tabulations will be performed for specific analysis populations. No imputation of values for missing data will be performed.

Statistical analyses will be primarily descriptive; no formal hypothesis testing will be conducted. Descriptive statistics will be provided for selected baseline, safety, and efficacy data by dose level and time point as appropriate.

In general, clinical data will be summarized for the dose escalation cohorts and for the dose expansion cohort, separately by each dose level where applicable, using descriptive statistics. Descriptive statistics for continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical presentation of selected data may also be performed. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. For selected assessments, confidence intervals (CIs) will be displayed.

13.1 Sample Size Considerations

Estimated sample sizes are calculated for the two primary outcome measurements: ADAS-Cog and GM atrophy (hippocampal). In order to ensure that the study has sufficient power to detect differences in both of the primary outcomes, the sample size chosen is the maximum of that calculated for each primary outcome.

The primary analysis was an intention-to-treat analysis and included all randomized participants. Data will be analysed using both Generalised Estimating Equations (GEE) and Bayesian Analysis.

The analysis of primary endpoints will use linear mixed-effects models, with random slopes and intercepts. For the ADAS-Cog, using mixed model analysis published estimates from the ADNI cohort[17] suggest a sample size of 125 AD participants per trial arm (total N = 250) will be required for power at 0.8 to detect a drug effect of 25% over two years and assuming a decline from baseline of 1.10 standardised units on the composite (SD change = 0.83).

For the MRI markers, Ledig *et al.* reported the sample sizes required for a 25% intervention reduction over two years based on 322 patients with AD (with 117 followed for 24 months) and a reduction of 10.2% (6.2) for hippocampus[18]. Sample size calculations based on hippocampal volume suggest that 93 subjects per treatment arm are required (total N = 186).

Assuming a 20% attrition rate, a sample of 314 subjects will be recruited for the Cognitive study, and 233 subjects will be randomly chosen for the Imaging study.

13.2 Analysis Populations

The safety population will include all patients who receive any amount of Investigational product (Lorelco ™ or placebo). The safety population will be used for all safety analyses.

The efficacy evaluable population will include all patients who receive any amount of Lorelco™ and who have completed a post-baseline disease response assessment. The efficacy evaluable population will be used for all efficacy analyses.

13.3 Demographic Data and Baseline Characteristics

Demographic data and baseline characteristics will be summarised using the safety population. Demographic data (including age, gender, race, ethnicity, body mass index, weight, and height) will be summarised using descriptive statistics. Medical history, surgical history, and prior medications will also be summarised.

13.4 Safety and Tolerability Analyses

Assessment of safety and tolerability is a seondary objective of the study. The analysis will assess the safety and tolerability of Lorelco™ in patients with mild to moderate AD using the safety population.

Safety and tolerability will be assessed through AE, clinical laboratory, vital signs, ECG, and physical examination data. AEs that occur at or after the first dose of Lorelco™ or placebo will be classified as treatment-emergent adverse events (TEAEs).

The original terms used in the eCRF by Investigators to identify AEs will be coded by system organ class and preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be grouped by system organ class and MedDRA preferred term and summarized by presenting the number and percentage of subjects who experience each TEAE and the number of TEAEs. Summaries by severity (graded according to the NCI-CTCAE v5.0 [or higher]) and relationship to Investigational Product will be provided for all TEAEs. Data listings will also be provided for any deaths, SAEs, and AEs leading to discontinuation of the study.

The actual values and changes from baseline at each post-baseline time point for clinical laboratory parameters, vital signs and ECG parameters will be summarized by visit and timepoint (where applicable). Where applicable, laboratory test results will be graded and summarized according to the NCI-CTCAE v5.0 (or higher). Baseline will be defined as the last assessment prior to the first dose of Lorelco™/ placebo.

13.5 Pharmacodynamic Analyses

Evaluation of pharmacodynamic parameters is an exploratory objective of this study. Pharmacodynamic marker parameters – observed data and change from baseline – will be summarized using descriptive statistics and graphs (mean ± SEM) per dose cohort, dose level and time interval as appropriate.

13.6 Efficacy Analyses

The primary analysis was an intention-to-treat analysis of all randomized participants. Data will be analysed using both Generalised Estimating Equations (GEE) and Bayesian Analysis. The analysis of primary endpoints will use linear mixed-effects models, with random slopes and intercepts.

The Alzheimer's Disease Assessment Scale's cognitive subscale (ADAS-Cog) is the standard primary cognitive outcome measure for evaluating treatments in clinical trials of mild-to-moderate AD. But the utility of ADAS-Cog is compromised primarily due to some of its items suffering from either floor or ceiling effects in different stages of AD. The current scoring methodology is also sensitive to missing item responses, scoring errors and variability in the administration of the ADAS-Cog, which are common in clinical trials.

The scoring methodology ADAS-Cog as proposed by Verma et al. will be utilised as it significantly improves the sensitivity of the ADAS-Cog in measuring progression of cognitive impairment in clinical trials focused in the mild-to-moderate AD stage[21]. This scoring methodology also provides a boost to the efficiency of clinical trials requiring fewer patients and shorter durations for investigating disease-modifying treatments. For patients with missing responses to certain items, this new scoring methodology does not require data imputation and estimates cognitive impairment using the set of items answered by the patients.

Analysis of all primary and secondary endpoints contrasting Probucol and placebo, after adjusting for covariates, will use mixed effects-regression with 'random' intercepts and slopes (as has been used for power calculations). Mean differences and associated 95% confidence intervals will be presented for the 'fixed' effect of Probucol treatment.

Further analysis investigating the relationship between change scores (post- minus pre-intervention scores) for the primary ADAS-Cog with MRI volumes (total GM, hippocampus, and medial temporal lobe volumes) and specific blood biomarkers (eg: plasma lipoprotein-Aβ) will be considered using Pearson (or Spearman where appropriate) correlation analysis. For all other correlations between recorded variables that lack an a priori hypothesis, control of statistical errors will be carried out using Holm-Sidak corrections for multiple comparisons.

If Probucol treatment is successful, a directed acyclic graph Bayesian network analysis will be carried out a posteriori on variables identified to be significant predictors of either GM arrest or neuropsychological performance to better elucidate mechanisms of the effect of Probucol. Greedy equivalence search will be used to identify statistical conditional dependencies between variables and directionality will be estimated using the linear, non-Gaussian, acyclic causal models (LiNGAM) approach[22,23]. Goodness of fit will be estimated using a $\chi 2$ test contrasting the identified model against a saturated model.

In addition to Bayesian analyses, the traditional General Linear Model analysis will also be utilised to compare Probucol to placebo, after adjusting for covariates. The Generalized

Estimating Equations method, which extends the generalized linear model to allow for analysis of repeated measurements or other correlated observations, will also be utilised.

Mean difference and associated 95% confidence intervals will be presented. Data will be analysed using Stata Version 16.

13.7 Primary Analysis

The primary analysis will occur when target enrolment is complete, and each patient either 104 weeks on study or withdraws.

13.8 Interim Analysis

No formal interim analyses are planned at this time. Safety will be reviewed in an ongoing fashion as described in Section 6.

14 DATA HANDLING AND RECORDKEEPING

14.1 Patient Identification and Enrolment Log and Patient Screening Log

The Investigator agrees to complete a patient identification and enrolment log to permit easy identification of each patient during and after the study. This document will be reviewed by the study monitor for completeness.

Any log identifying study patient identity will be treated as confidential and will be filed by the Investigator in the Investigator Site File (ISF). To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by initials and assigned number only.

The Investigator must also complete a patient screening log, which reports on all patients who were seen to determine eligibility for inclusion in the study.

14.2 Source Documentation

At a minimum, source documentation must be available to substantiate patient identification, eligibility, and participation; proper informed consent procedures; protocol specified medical history; dates of visits; adherence to protocol procedures; records of safety and efficacy parameters; adequate reporting and follow-up of AEs; administration of concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of patient completion, discontinuation from treatment, or withdrawal from the study, and the reason if appropriate. Specific items required as source documents will be reviewed with the Investigator before the study.

The author of an entry in the source documents must be identifiable. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the patients' source documentation.

Following the ICH-GCP guidelines, direct access to source documentation and medical records must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

14.3 Case Report Form

An eCRF entry must be completed for each patient who is successfully enrolled (received at

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least one dose of study drug). For reasons of confidentiality, the name and initials of the patient should not appear in the eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

Data entry into the eCRF will be conducted throughout study conduct according to the Sponsor's (or designee) instructions and reviewed by the Sponsor (or designee) to determine their acceptability. If necessary, eCRF queries will be raised by the Sponsor (or designee) relating to eCRF data entries. The Investigator or authorized study site staff must address all eCRF queries raised.

14.4 Retention of Records

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all source documents that support the data collected from each patient, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial. The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Following closure of the study, the PI must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. When permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The PI must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the PI must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Essential documents must be retained as per the applicable regulatory requirements for the country where the site is located or by an agreement with the sponsor. Curtin University, will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Curtin University, standards/procedures; otherwise, the retention period will default to 15 years.

The material to be stored shall include, but is not limited to, the following:

- Signed and dated copy of the HREC approved study protocol and any HREC approved amendments;
- Signed and dated letter of HREC approval, letter of constitution of the HREC and copies of any other correspondence relevant to the study with the HREC or regulatory authorities;
- The HREC approved ICF;
- Current Curriculum Vitae (signed and dated) of the PI and co-workers with major responsibilities in the trial;
- Site Signature and Delegation of Responsibility Log;
- Financial Disclosure Form(s);
- Blank eCRF;

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- Signed participant ICF;
- Laboratory reference ranges (signed and dated);
- The final CSR;
- Clinical raw data including the Source Data Forms, all clinical laboratory report forms, participant eCRF, drug accountability forms, and dispensing records, etc.

It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate Regulatory Authority to review any documentation relating to this study, the Investigator must permit access to all study documentation.

15 ETHICS AND REGULATORY COMPLIANCE

15.1 Investigator Responsibilities

The Investigator agrees to conduct the clinical study in accordance with the protocol, current ICH guidelines for GCP, and applicable regulatory and legal requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

15.2 Ethics Approval

Prior to initiation of the study, written HREC approval of the Protocol and Participant Information and Consent Forms, based on the principles of ICH GCP procedures, will be received. This approval will be typed on the Institutional letterhead and will refer to the Participant Information and Consent Forms and to the study Protocol by title and protocol number and will also include date of each document. A copy of the signed and dated letter of approval will be provided to the Australian Alzheimer's Research Foundation and Curtin University, prior to study commencement. Any written information and/or advertisements to be used for patient recruitment will be approved by the HREC prior to use. A list of the HREC voting members, their titles or occupations, and their institutional affiliations will be requested before study initiation.

Protocol modifications that may impact on participant safety or the validity of the study will be approved by HREC, following written agreement from the Sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the HREC. The records should be filed in the Investigator's Trial File and copies must be sent to the Sponsor and maintained in the study Trial Master File.

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15.3 Regulatory Notification

The requirements for the conduct of clinical trials in accordance with the applicable regulations of the Australian Therapeutic Goods Administration (TGA) under the Clinical Trial Notification (CTN) scheme must be met before commencement of this study.

15.4 Ethical Considerations

This study will be carried out according to the principles of the Declaration of Helsinki, the ICH guidelines for GCP (as adopted in Australia) and the National Statement on Ethical Conduct in Human Research, (2007 incorporating all updates).

The Protocol has been approved by Bellberry HREC (HREC2019-11-1063). The composition of the HREC will also be provided to the Sponsor. If approval is suspended or terminated by the HREC, the PI will notify the Sponsor immediately.

The Sponsor, Curtin University, agree to abide by the Medicines Australia Guidelines for compensation for injury resulting from participating in a company-sponsored research project.

Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability and is participant to the proposed recipient signing a full and complete release of the company from all claims, damages and costs.

15.5 Informed Consent

Informed consent will be obtained before any patient can participate in the study. The consent form must be signed before performance of any study-related activity. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements and adhere to ICH GCP guidelines and the requirements in the Declaration of Helsinki. Study participation includes any and all screening and training procedures, as well as any wash-out of excluded medications.

It is the responsibility of the PI or the delegate who conducted the informed consent procedure to obtain a voluntary signed and dated informed consent from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The PI (or delegate) must also explain to the patients that they are completely free to refuse to enter the study or to withdraw from it at any time. All eligible patients must receive a full explanation, in layman's terms, of the aims of the study, the discomfort, risks and potential benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each patient will acknowledge receipt of this information by giving written informed consent for participation in the study. The Participant Information and Consent Form must also be signed and dated by the person who conducted the informed consent procedure. All patients will be given a copy of the signed Participant Information and Consent Form to retain.

Should a protocol amendment become necessary, the Participant Information and Consent Forms may need to be revised to reflect the changes to the protocol. It is the responsibility of

the Sponsor designee to ensure that an amended Participant Information and Consent Form is reviewed and has received favourable opinion from HREC, and the Investigator has to ensure that the amended consent form is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment

15.6 Emergency Contact with Principal Investigator

Suitable arrangements will be made for patients to make contact with the PI or medically trained nominee in the event of an emergency.

15.7 Pandemic Preparedness

Clinical sites should have in place procedures and strategies to accommodate the current COVID-19 pandemic (or other pandemics as appropriate). Such procedures should include requirements in relation to criteria such as:

- Attendance (e.g. who is permitted to be on site during a pandemic, limitations, records of attendance, plans for suppliers and deliveries);
- Physical layout (e.g. physical distancing requirements and signage);
- Flexibility (e.g. procedures for scaling, ability to respond to outbreaks);
- Support for remote interactions with Sponsors and study teams (e.g. communication including infrastructure);
- The local environment (e.g. contact with local Health Authorities, ability to access up-to-date pandemic information);
- Any other relevant criteria.

It is noted that COVID-19 testing may be performed at any stage during the trial for any patient who is clinically indicated as per the Investigators discretion and/or as directed by Local Health Authorities.

15.8 Notification of the General Practitioner

It is the responsibility of the PI or nominee, to notify, where applicable, the patient's General Practitioner of the patient's participation in the trial. This notification should be by sending a letter stating the nature of the trial, treatments, expected benefits or AEs and concomitant drugs to be avoided. The consent of the patient should be sought prior to contacting their General Practitioner.

15.9 Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the PI, or nominee, will obtain a copy of the certification form, with certification number and expiration date for all clinical laboratories used in the study. Reference ranges for each clinical laboratory test used in this study will be obtained from the appropriate laboratory, which will perform the test for the study.

15.10 Privacy of Personal Data

In order to maintain patient privacy, all eCRF, study drug accountability records, study reports and communications will identify the patient by their assigned patient number. The Investigator will grant monitor(s) and auditor(s) from Curtin University (or designee) and Regulatory Authorities access to the patient's original medical records for verification of data gathered on the eCRF and to audit the data collection process. The patient's confidentiality

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will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.11 Study Completion/Site Closure

The study is considered completed at the last contact of the last patient involved in the study. The final data from the investigational site will be sent to the Sponsor (or designee) in the time frame specified in the Clinical Trial Research Agreement. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed by the sponsor (or delegate).

15.12 Termination of the Study

The Sponsor reserves the right to discontinue the trial at any time. Reasons will be provided in the event of this happening. The PI reserves the right to discontinue the study for safety reasons at any time in consultation with the Sponsor.

15.13 End of Study and Regulatory Notification

At the end of the study, the HREC and relevant Regulatory Authorities (TGA) will be notified by the Sponsor (or delegate) according to applicable regulatory requirements.

16 QUALITY CONTROL AND ASSURANCE

16.1 Study Monitoring

During the course of the trial, the Sponsor or designee will visit the study site and/or perform remote monitoring at regular intervals and must be available for discussions by telephone. The purpose of the monitoring visits is to ensure that the eCRF is completed correctly and the protocol adhered to, to perform source data verification and monitor drug accountability.

The study monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to evaluation of the study.

The Sponsor is responsible for assuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded in the eCRF. Participant confidentiality will be maintained.

In accordance with applicable regulations and ICH GCP, Australian Alzheimer's Research Foundation (contracted by Curtin University), will be responsible for assigning a study monitor who will contact the site to organise a visit prior to patient enrolment to review the protocol and data collection procedures with site staff. In addition, the assigned study monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

During these site visits, the study monitor will:

- Check the progress of the study;
- Review study data collected;
- Conduct source document verification;

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- Identify any issues and address their resolution;
- Check study drug accountability;
- Review biological samples collected for the study and ensure they are labelled and stored correctly;
- Verify that:
    - The data are authentic, accurate and complete;
    - Safety and rights of participants are being protected;
    - Study is conducted in accordance with the currently approved protocol (and any amendments), ICH GCP and all applicable regulatory requirements.

The PI agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, a study monitor will conduct the following activities in conjunction with the PI or site staff as appropriate:

- Return of all study data to Curtin University;
- Resolving all data queries;
- Accountability, reconciliation and arrangements for unused study drug(s);
- Inventory and final disposition (e.g., destruction, shipping to repository, etc.);
- Review of site study records for completeness.

16.2 Quality Assurance and Quality Control

To ensure compliance with ICH GCP and all applicable regulatory requirements, Curtin University (or a designated third party), may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and Institution agree to notify the Sponsor as soon as possible following awareness of an impending regulatory inspection. The Investigator and Institution agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The Sponsor (or its designee) will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator (and delegate(s)) generating the data.

Prior to the study initiation, the Sponsor (or its designee) will explain the protocol, Investigator's Brochure, and eCRF to the Investigator and the site staff involved in this study. In addition, the assigned study monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

16.3 Data Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centres, review of protocol procedures with the Investigator and associated personnel before the study, and periodic monitoring visits by the Sponsor (or designee). Written instructions will be provided for collection, preparation, and shipment of whole blood. eCRF completion training will be conducted with study personnel

before the start of the study. The Sponsor's monitor will review electronic data for accuracy and completeness during onsite monitoring visits and after his/her return to the Sponsor's office; any discrepancies will be resolved with the Investigator or designee, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

17 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate Clinical Trial Research Agreement.

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

Curtin University will be subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating patients and arising out of this research performed strictly in accordance with the study protocol as well as with applicable law and professional standards prior to the dosing of the first patient.

18 STUDY PROTOCOL GUIDELINES

18.1 Protocol Deviations and Violations

A protocol deviation is an accidental or unintentional change to, or non-compliance with the HREC approved protocol that does not increase risk or decrease benefit; does not have a significant effect on the patient's rights, safety or welfare, or the integrity of the data. No deviations to the protocol are permitted, except in instances when an emergency occurs that requires a departure from the protocol for a patient. The nature and reasons for the protocol deviation will be recorded in the clinical trial management system (CTMS) and reported at the end of the study in the clinical study report. Should a non-anticipated protocol deviation occur, the Sponsor must be informed as soon as possible.

A protocol violation is an accidental or unintentional change to, or non-compliance with the HREC approved protocol (without prior Sponsor and HREC approval), which increases the risk or decreases the benefit, affects the participant's rights, safety, or welfare, or the integrity of the data. Reporting of protocol violations to the HREC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

All deviations (or violations), and the reasons for the deviation (or violation) will be documented by the PI or designated staff.

18.2 Protocol Waivers

Protocol waivers will not be granted by the Sponsor in this study.

18.3 Protocol Amendments

Administrative amendments to the protocol will be classed as amendments of typographical errors, clarifications of confusing wording, and other minor modifications including but not limited to name, address, and contact information changes that have no impact on the safety of the participant or the science of the study. Administrative amendments will be submitted to the HREC for information only. The Sponsor (or designee) will ensure that acknowledgement is received and filed. Otherwise, an amendment will be classed as a substantial amendment

and will be submitted to the appropriate Regulatory Authorities and the HREC for approval.

19 INTELLECTUAL PROPERTY, CONFIDENTIALITY AND PUBLICATIONS

19.1 Ownership

All information provided by Curtin University and all data and information generated by the clinical facility staff as part of the study (other than a patient's medical records), are the sole property of Curtin University.

All rights, title and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by clinical facility staff during the course of or as a result of the study are the sole property of Curtin University and are hereby assigned to Curtin University.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between Curtin University and the clinical facility that contract's ownership provisions shall apply rather than this statement.

19.2 Confidentiality

All information provided by Curtin University and all data and information generated by the clinical facility as part of the study will be kept confidential by the PI and other site staff. The PI or other site personnel will not use this information and data for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the PI or site staff; (2) information which it is necessary to disclose in confidence to a HREC solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study participant; or (4) study results which may be published as described in the Publication Policy section (section 19.3). If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

19.3 Publication Policy

Curtin University, plans to publish the results of this study at an appropriate time. No publication of the results shall take place without the express consent of Curtin University. Prior to submitting for any publication, presentation, use for instructional purposes or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the PI shall provide Curtin University with a copy of the proposed publication and allow Curtin University a period of at least thirty (30) days [or for abstracts, at least fifteen (15) working days] to review the proposed publication. Proposed publications shall not include Curtin University confidential information.

At the request of Curtin University the submission or other disclosure of a proposed publication will be delayed for a sufficient length of time to allow Curtin University to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with the statement is executed, that contract's publication provisions shall apply rather than this statement.

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21 APPENDICES

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21.1 APPENDIX 1. Overall Schedule of Assessments

STUDY PERIODS►	Screening	PRE-BASELINE- Visit 0	BASELINE Visit 1																		
OUTPATIENT VISIT►	X	X	X	X	X		X		X		X		X		X		X		X	X	X
TELEPHONE CALL►						X		X		X		X		X		X		X			
STUDY DAY►	Day -56 - Day-1	Week 1- Week 3	Week 3 Day1	Week 4	Week 5	Week 6	Week 15	Week 20	Week 26	Week 29	Week 39	Week 47	Week 52	Week 55	Week 65	Week 73	Week 78	Week 81	Week 91	Week 104	Week 108
WINDOW►		± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 7 Days	± 2 Days	± 2 Days	± 2 Days	± 7 Days	± 2 Days	± 2 Days	± 2 Days	± 7 Days	± 2 Days	± 2 Days	± 7 Days	±2 weeks
Informed Consent	X																				
Incl. Excl Criteria[1]	X	X	X																		
Demographics	X																				
Medical & Disease History	X																				
Concomitant Medications[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment History	X																				
Physical Examination[3]	X			x	x		X		X		X		X		X		X		X	X	X
Neurological Examination[3]	X			X	X		X		X		X		X		X		X		X	X	X
Vitals[4]	X			x	x		X		X		X		X		X		X		X	X	X
ECG[5]	X		X	x	x		X		X		X		X		X		X		X	X	X
Pregnancy hCG Test[6,7]	X		X				X		X				X				X		X		
Full haematology/ serum chemistry panel[8,9]	X		X	X	X		X		X		X		X		X		X		X	X	X
Apolipoprotein E (ApoE) genetic testing[8]	X																				
MMSE	X																			X	
FCSRT	X																				
CDR	X																				
ADAS-Cog			X						X				X				X			X	
DASS-21		X							X											X	
ADCS-MCI-ADL24[10]		x							X											X	
PET scan/MRI[11]	X	X																		X	
Randomisation		X																			
Dispense		X	X	X	X		X		X		X		X		X		X		X		

Probucol/Placebo[12]																					
Probucol / Placebo[13]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Probucol/Placebo compliance check	x		x	x	x		x		x		x		x		x		x		x	x	
Adverse Events[14]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Note. ECG = electrocardiogram, EOS= End of Study, ET= Early Termination, MMSE = Mini Mental State Examination, FCSRT = Free and Cued Selective Reminding Test, CDR = Clinical Dementia Rating, ADAS-Cog = Alzheimer's Disease Assessment Scales-Cognitive Subscale test, DASS-21 = Depression, Anxiety, and Stress Scale -21, ADCS-MCI-ADL24 = Alzheimer's Disease Co-operative Study Mild Cognitive Impairment Activities of Daily Living. Details of Assessments are in the body of the protocol.

Notes: Overall Schedule of Assessments

1	Eligibility (including medical history, staging, and concomitant medication usage) to be reviewed, and eligibility confirmed prior to dose administration on Day 1.
2	Concomitant medication usage to be reviewed by study staff at each scheduled visit and telephone call
3	Full physical examination at Screening and End of Study visit to include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, lymph nodes, heart, chest, abdomen and extremities, and a neurological examination (assessment of speech, cranial nerves, motor power, deep tendon reflexes, sensation, coordination and gait), and any other focused assessments suggested by the presence of specific symptoms. All abnormal findings noted at the screening visit should be recorded as medical history. All other physical examinations will be abbreviated on symptom directed at the discretion of the investigator
4	Participants should be resting in a supine position for at least 5 minutes prior to and during vital signs measurements. Vital sign assessments may be repeated once, if abnormal values were recorded in the first instance, at the discretion of the PI.
5	ECGs will be taken after at least 5 minutes in a supine quiet rest position. Screening and prior to first dose, triplicate 12-lead ECGs (within 5 minutes, with each reading separated by at least 1 minute) will be taken to establish baseline. The average value for the triplicate will be utilized for assessing QTcF inclusion criteria. Triplicate 12-lead ECGs will also be recorded at the EoS visit. All other post-first dose ECGs will be single readings. In case of evident bad quality (e.g. muscle tremor) of the tracing, the ECG will be repeated.
6	For women of childbearing potential only. Testing must be performed, and confirmed negative (hCG ≤5 U/L), prior to dose administration.
7	For women of childbearing potential only. If the hCG blood test is > 5 U/L but < 25 U/L, repeat hCG test will be completed after 7 days.
8	Patients are required to fast for a minimum of 8 hours prior to blood sample collection. Water is permitted. Fasting blood tests include serum thyroid, CRP, iron studies, B12, folate, blood sugar, HbA1c and lipids (refer to APPENDIX 5).
9	Haematology, serum chemistry and coagulation tests will be performed (refer to APPENDIX 5). Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible TEAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. Pre-dose safety laboratory blood samples scheduled for Cycle 1 Day 1 do not need to be repeated if screening blood tests were performed within 4 days prior to study drug administration.
10	ADCS-MCI-ADL24 will be completed by the study partner.
11	Standard MRI/PET imaging assessments will be performed during screening and at the EoS visit
12	Supply of Lorelco™ or placebo to be provided to the patient for at-home dosing in a Webster pack, with amount provided to last a full cycle.
13	Patients to self-administer Lorelco™ or placebo at home, per protocol.
14	Adverse events to be monitored throughout the duration of the study.

21.2 APPENDIX 2: Clinical Laboratory Assessments

Haematology	**Serum Chemistry, Including Liver Function**	**Fasting bloods (to be collected at each visit)**
Hemoglobin Hematocrit RBC indices Thrombocyte count (platelets) Reticulocyte count WBC count with differential: Neutrophil count Eosinophil count Basophil count Lymphocyte count Monocyte count	Sodium Potassium Chloride Bicarbonate Phosphate Calcium Magnesium Lipase Uric acid Albumin Globulins Protein LDH Creatine kinase Creatinine (including calculated CrCl using Cockcroft-Gault formula) Urea ALP ALT AST GGT Total bilirubin Conjugated and unconjugated Bilirubin TSH T4 T3	CRP Blood glucose levels Total cholesterol HDL LDL Triglycerides.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; TSH = thyroid stimulating hormone; T4 = Thyroxine; T3 = triiodothyronine; CRP = C-reactive protein; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RBC = red blood cell; WBC = white blood cell.		

21.3 APPENDIX 3: Acceptable Forms of Highly Effective Contraception

Examples of acceptable forms of highly effective contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Sterilised male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- True abstinence: When this is in line with your preferred and usual lifestyle.

Examples of non-acceptable methods of contraception include:

- Condoms alone or double barrier.
- Periodic abstinence (e.g. calendar, ovulation, sympthothermal, post ovulation).
- Withdrawal.

21.4 APPENDIX 4: List of QT prolongation Inducers

The following table is prepared to provide examples of clinical inhibitors and inducers and is not intended to be an exhaustive list. For an up-to-date listing, please refer to eMIMS Australia (www.emims.com.au) or the Australian Medicines Handbook (https://amhonline.amh.net.au/auth)

Table 5. Overview of Clinical QT prolongation Inducers

• erythromycin • chloroquine • disopyramide • flicanide • isoprenaline • procainamide • quinidine • antipsychotics

Note: **Strong** QT prolongation inducers are **not** allowed in this clinical trial.

Source: https:/www.emims.com.au

Lam V, *et al. BMJ Open* 2022; 12:e058826. doi: 10.1136/bmjopen-2021-058826