1. TITLE PAGE

Neurim Pharmaceuticals (1991) Ltd
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STUDY NUMBER: NEUP11-7 (PIROAD)

CLINICALTRIALS.GOV ID: NCT05267535

RANDOMIZED, DELAYED START, DOUBLE BLIND, PARALLEL GROUP, PLACEBO CONTROLLED, MULTICENTER STUDY OF PIROMELATINE 20 MG IN PARTICIPANTS WITH MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE

PHASE: 2/3

CONFIDENTIAL

CRO: Syneos Health, LLC

DATE OF PROTOCOL: 22 January 2023

STATUS OF PROTOCOL: Final

2. APPROVAL SIGNATURES

RANDOMIZED, DELAYED START, DOUBLE BLIND, PARALLEL GROUP, PLACEBO CONTROLLED, MULTICENTER STUDY OF PIROMELATINE 20 MG IN PARTICIPANTS WITH MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE

Protocol No. NEUP11-7

CLINICALTRIALS.GOV ID: NCT05267535

NEURIM PHARMACEUTICALS (1991) LTD

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Date: 22 January 2023

Tali Nir, DVM
VP, Clinical and Regulatory Affairs
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SPONSOR'S SAFETY OFFICER

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Ksenia Shapiro, M.Pharm, BioMed MBA
Head of Global Quality & Pharmacovigilance
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ISRAEL

INVESTIGATOR

I have carefully read the foregoing protocol, including all appendices, and agree that it contains all the necessary information for conducting the study safely.

I will conduct the study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) guidelines and will attempt to complete the study within the designated time.

I will provide copies of the protocol and all other information relating to the preclinical and prior clinical experience submitted by the sponsor (Neurim Pharmaceuticals [1991] Ltd) to all study personnel. I will discuss this information with them to assure they are adequately informed regarding the drug and the conduct of the study.

I agree to keep records on all patient information (case report forms, shipment and drug return forms, and all other information collected during the study) in accordance with the current GCP and local regulations.

_____	Dr. Tali Nir, DVM
Principal Investigator	Sponsor Representative
_____	_____
Signature	Signature
_____	_____
Date	Date

_____

Name of Site

3. SUMMARY/SYNOPSIS OF PROTOCOL

STUDY NUMBER	NEUP11-7
STUDY DRUGS **Test drug** **Control drug**	 Piromelatine 20 mg tablets Matched placebo tablets
TITLE	Randomized, delayed start, double-blind, parallel group, placebo controlled, multicenter study of piromelatine 20 mg in participants with mild dementia due to Alzheimer's disease
STUDY PHASE	2/3
COUNTRIES	North America (NA) and Europe (EU)
ESTIMATED NUMBER OF CENTERS	Approximately 30 sites
STUDY RATIONALE	Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the leading cause of dementia in the elderly population. Effective treatments for the devastating disease are urgently needed as the world's population continues to age. The diagnosis of AD is generally based on consensus diagnostic criteria developed by the National Institute on Aging-Alzheimer's Association (NIA-AA) (McKhann, Knopman et al. 2011). These criteria are clinical in nature and require that patients must exhibit impairments in both cognitive and functional domains. In the earliest clinical stages of AD, subtle cognitive deficits may be evident only through use of sensitive measures of neuropsychological performance. Thereafter, but before developing overt dementia, patients proceed through a clinical phase where cognition becomes increasingly affected and relatively mild but detectable impairments in some functional abilities emerge as well. The presence of extracellular β-amyloid deposition as neuritic plaques and intracellular accumulation of hyperphosphorylated tau as neurofibrillary tangles remains the primary neuropathologic criteria for AD diagnosis (Long and Holtzman 2019). However, numerous phase 3 clinical trials, aimed at the abnormal production and aggregation of Aβ have failed to improve neuropsychological performance and functional abilities, and slow down disease progression. Recently aducanumab has received conditional US FDA approval for disease modification based upon surrogate endpoint outcomes (amyloid lowering). **Piromelatine** The investigational compound, N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-4-oxo-4H-pyran-2-carboxamide (piromelatine) is a novel

	melatonin MT1, 2, and 3 and serotonin 5-HT-1A and -1D receptors agonist with a different proposed mechanism of action than currently available AD medications. Simultaneous activation of melatonergic and 5HT-1a receptors may synergistically promote neurogenesis (Fava, Targum et al. 2012). Melatonin receptor agonism, which maintains the NREM SWS (Arbon, Knurowska et al. 2015), appears beneficial for cognition and functioning in mild to moderate AD patients (Wade, Farmer et al. 2014). Through this unique molecular mode of action, piromelatine demonstrated in preclinical studies in rodents neuroprotective (Tang, Wang et al. 2012, Buendia, Navarro et al. 2014), memory enhancing (Tian, Laudon et al. 2010, He, Ouyang et al. 2013), sleep promoting (Liu, Yin et al. 2014), and neurogenic capabilities (Tian et al., 2015 unpublished) with relevance to AD risk factors, comorbidities, and symptoms. **Clinical Studies** In a Phase 1 study in healthy volunteers, piromelatine (2, 5, 20, 50, and 200 mg) was found to be safe and well tolerated with no serious adverse events (SAEs) and showed a favorable, dose-proportional pharmacokinetic (PK) profile following oral intake. In addition, piromelatine intake was associated with increase in fatigue and total sleep time in the volunteers in a dose-dependent manner (Yalkinoglu, Zisapel et al. 2010). In a Phase 1b multiple ascending dose study in insomnia patients, piromelatine (2, 5, 20, and 50 mg) had a favorable PK profile without any sign of accumulation. Importantly, in this study piromelatine administered for 5 days to non-demented patients with insomnia had no detrimental nor beneficial effect on learning and memory as measured using the word-pair association task (Laudon, Katz et al. 2012). In a Phase 2, randomized, placebo-controlled, sleep laboratory study in insomnia patients (n=137 aged 18-80), piromelatine (20 mg and 50 mg daily for 1 month) enhanced sleep maintenance (wake after sleep onset [WASO]) measured by polysomnography (PSG) significantly in comparison to placebo (Neurim press release, 2013). The 20 mg was found fully effective for the age 55 year and over patients. Piromelatine enhanced NREM Δ power (NREM SWS) and decreased NREM β power, a fast electroencephalogram (EEG) activity that is considered to be related to the hyperarousal state experienced by insomniac patients (Merica, Blois et al. 1998). Both effects may be beneficial for early AD and AD patients to enhance Aβ clearance from the brain (Grandy 2013). Overall, piromelatine was generally safe and well tolerated. There were no SAEs during the conduct of this study. Adverse event (AE) rates during double-blind treatment with study medication were low (6.7% in the piromelatine 20 mg group, 0% in the piromelatine 50 mg and placebo groups). Laboratory values were within normal ranges. No clinically meaningful changes in vital signs, electrocardiograms (ECGs), or physical examinations were observed. No suicidal behavior or suicidal ideation (Columbia Suicide Severity Rating Scale [CSSRS]) was recorded at any time during the study.

	In a Phase 2, randomized, placebo-controlled, dose-ranging study (ReCognition) of piromelatine (5, 20, and 50 mg daily for 6 months) in participants with mild dementia due to Alzheimer's disease (n=352 age 60-85 years), no safety concerns were observed and no specific trends in AEs by treatment group or piromelatine dose were noted. The incidence of the TEAEs observed in the placebo group (48.6%) was similar to the incidence observed in the piromelatine groups (44.3% in the 5-mg group, 56.8% in the 20-mg group, and 39.1% in the 50-mg group). The most frequently reported TEAE was headache in 19 patients (5.2%) with 34 events in total, followed by nasopharyngitis in 18 patients (4.9%) with 20 events. However, there were no statistically significant differences between the placebo and piromelatine groups in the changes from baseline in the primary endpoint (global composite score of the computerized Neuropsychological Test Battery (cNTB) secondary, or exploratory parameters (Clinical Global Impression of Change (CGIC), Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) patients (ADCS-MCI-ADL), Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog14) or Pittsburgh sleep quality index (PSQI)). **Genome wide association study (GWAS)** A Genome wide association study (GWAS) of a representative sample (N=107) of the ReCognition study cohort identified an association between enhancement with piromelatine in cognitive functioning as assessed by cNTB and the presence of 5 to 6 single nucleotide polymorphisms in chromosome 2, 2:107,510,000-107,540,000 locus (2:107,510,000-107,540,000 polymorphism). SNPs in this locus, reportedly present in ca. 17% of the global population (www.niagads.org/genomics/) was present in 27% of participants with mild dementia due to Alzheimer's disease in the ReCognition study. In a subsequent post hoc analysis it was found that the participants with 2:107,510,000-107,540,000 polymorphism had significant worsening on ADAS-Cog14 and PSQI with piromelatine 20 mg compared to placebo. There was no interaction with APOE4 genotype. The worsening in ADAS-Cog14 in participants with 2:107,510,000-107,540,000 polymorphism was significantly correlated with the worsening in PSQI (R=0.56; p=0.029). Hypnotic drugs, e.g. benzodiazepines, may have alerting effects in some subjects (Mancuso, Tanzi et al. 2004, Akeju and Brown 2013, Jordahn, Andersen et al. 2016). Association between deterioration in cognition from healthy controls through MCI to AD patients and deterioration in sleep has been reported (Economou, Papageorgiou et al. 2013). Accordingly, the worsening in ADAS-Cog14 in participants with 2:107,510,000-107,540,000 polymorphism may be linked to an unwanted increase in alertness with piromelatine. This worsening calls for exclusion of 2:107,510,000-107,540,000 polymorphism carriers from future studies of piromelatine in mild dementia due to Alzheimer's Disease.

	By contrast, in participants without 2:107,510,000-107,540,000 polymorphism (73% of the ReCognition study cohort), piromelatine 20 and 50 mg improved ADAS-cog14 (effect sizes 0.63) compared to placebo. Improvement was greater with time against worsening in the placebo arm. PSQI also improved significantly with piromelatine 20 and 50 mg compared to placebo (effect sizes 0.66). Considerable effects sizes of piromelatine (0.36-0.42) were found also for MMSE and CGIC. The 20 mg dose was sufficient to evoke the full response. Overall, piromelatine appears efficacious and safe in mild dementia due to Alzheimer's Disease in participants who do not have 2:107,510,000-107,540,000 locus polymorphism. **Proposed Trial** Based on the above, this study of piromelatine 20 mg versus placebo in participants with mild dementia due to Alzheimer's disease is conducted as a confirmatory, randomized efficacy and safety study in participants who are 2:107,510,000-107,540,000 polymorphism non-carriers (N=225). Participants will be randomized in a 1:1 allocation ratio to receive either piromelatine 20 mg or placebo for 26 weeks. Medication is to be administered orally, one tablet daily, taken 1-2 hours before going to bed (preferably between 2100h and 2200h) and after food. To differentiate between symptomatic effects and potential disease modifying effects of piromelatine, there will be a delayed-start open-label extension period of 12 months treatment wherein placebo-treated participants will be treated with piromelatine (20 mg daily) and the piromelatine-treated patients will be continued. This exploratory phase is aimed to continue randomized assignment of piromelatine treatment, long-term (18 months overall) to evaluate its potential disease modifying effect compared to patients in the placebo-randomized group who started the treatment after a 6-month delay. The primary efficacy analysis (blinded) is planned after completion of the 26 weeks double blind period. If efficacy is not confirmed, then the study will be ended without completing the extension period.
PRIMARY OBJECTIVES	To compare the effect of piromelatine (20 mg daily) to that of placebo on the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog14) at Week 26 of double-blind treatment
KEY SECONDARY OBJECTIVES	To compare the effect of piromelatine (20 mg) to that of placebo on the Alzheimer's Disease Cooperative Study - Instrumental Activities of Daily Living (ADCS-iADL) at week 26 of double--blind treatment
SECONDARY OBJECTIVES	1. To compare the effect of piromelatine (20 mg daily) to that of placebo on global impression assessed by the ADCS-Clinical

	Global Impression of Change (CGIC) at Week 26 of double-blind treatment 2. To compare the effect of piromelatine (20 mg) to that of placebo on cognitive aspects of mental function assessed by the Mini-Mental State Examination (MMSE) at Week 26 of the double--blind treatment 3. To compare the safety and tolerability of piromelatine (20 mg) to that of placebo over 26 weeks of double-blind treatment
OTHER SECONDARY OBJECTIVES	4. To compare the effect of piromelatine (20 mg) to that of placebo on behavioral signs and symptoms assessed by the Neuropsychiatric Inventory (NPI) scale after 26 weeks of double-blind treatment 5. To compare the effect of piromelatine (20 mg) to that of placebo on sleep variables derived from the PSQI at Weeks 13, and 26 and over 26 weeks of double-blind treatment
EXPLORATORY ENDPOINTS	1. Long-term safety and efficacy of 18 months piromelatine 20 mg compared to end of the double-blind period. 2. Disease modifying potential comparing a) Difference from baseline in mean ADAS-cog14 in the early and delayed start groups by 52 and 78 weeks of treatment. b) Difference from baseline in mean MMSE, CDR_SB scores in the early and delayed start groups by 78 weeks of treatment. c) Rate of progression in the 26 weeks extension period and the first 26 weeks randomized period for each group (ADAS-cog14, MMSE, ADCS-iADL).
STUDY DESIGN	This study in participants with mild dementia due to Alzheimer's disease is conducted as a confirmatory, randomized efficacy and safety study of 20 mg piromelatine versus placebo in participants who are 2:107,510,000-107,540,000 polymorphism non-carriers and as an exploratory study of potential disease modifying effects of the drug. Patients with a documented history of **mild dementia due to AD for at least 12 months,** having an MMSE score of 20 to 26 (inclusive) at Screening (, and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1 will be recruited and further screened for eligibility. Informant commitment for the study is also necessary. At Screening (Visit 1), patients will undergo neuropsychiatric assessments, psychometric testing, and general medical assessments (including medical history, pre-existing conditions, physical examination, vital signs, and ECG). If patients have not had brain imaging with findings consistent with the diagnosis of dementia due to AD in the last 12 months, a magnetic resonance imaging (MRI) scan or CT will be obtained to rule out clinically significant comorbid pathologies. A whole genome sequencing will be obtained for 2:107,510,000-107,540,000 polymorphism. In addition, plasma

	biomarkers assessment will be done using the high amyloid probability score (APS) by the PrecivityAD™-Aβ blood test which will also provide APOE3/4 and pTau 181 / 217 presence in plasma. Assuming an effect size between treatment dose and placebo of 0.51 over 26 weeks in ADAS-Cog14 for participants who are 2:107,510,000-107,540,000 polymorphism non-carriers, a significant level (α) of 0.05, and power of 90%, a sample size of 83 patients/arm is calculated. Assuming a 25% screen failure rate and 25% 2:107,510,000-107,540,000 polymorphism carriers and allowing for 26% patient withdrawal, 400 patients should be screened in order to randomly assign 225 2:107,510,000-107,540,000 polymorphism non-carrier patients, of whom 166 would be expected to complete the 26 weeks period. Allowing for another 24% patient withdrawal during the open-label long term study, 126 patients will complete the 80 weeks period. After confirmation of eligibility from the Clinical Surveillance & Training team (CST) and up to 4 weeks after the screening visit, eligible patients will start a 2 week run in period of placebo (single blind), followed by 26 weeks of double blind treatment comprising administration of piromelatine or placebo in a 1:1 randomization ratio, for a total treatment duration of 28 weeks.. Because of expected differential clinical course and amyloid load, APOE4 carriers randomization will be stratified by APOE4 carrier status measured by the Precivity test. Visits in the double-blind phase will be carried out at 13 weeks (Visit 3) and 26 weeks (Visit 4) after randomization (Visit 2). There are 3 assessments in the extension period at 39 (Visit 5), 52 (Visit 6) and 78 weeks (Visit 7) after randomization. A follow-up phone call to assess adverse events and safety will be completed 2 weeks after the last dose of study medication. An efficacy analysis (blinded) is intended after completion of the 26 weeks double blind period; if efficacy is not confirmed, the study will be terminated without completing the extension period. Patients who discontinue medication treatment prior to Visit 4 (Week 26) will be brought back for a termination visit as soon as possible after termination and not later than week 26. Piromelatine and placebo will be administered orally, once daily after a meal, before habitual bedtime, preferably between 2100h and 2300h. Patients will be required to spend at least 2 hours a day exposed to daylight.
STUDY DURATION	The study consists of a 6-week screening and run--in period:4 4 weeks without treatment (screening) and 2 weeksof single--blind placebo (run-in period), followed by a 26 -week, randomized, double-b-lind treatment period comprising administration of piromelatine or placebo, for a total treatment duration of 28 weeks. An extension period will follow of open label piromelatine 20 mg for 12 months to evaluate potential disease modifying effects.

	A follow--up phone call to elicit any adverse events and safety concerns will be completed 2 weeks after the last dose of study medication.
STUDY POPULATION	Male or female patients with mild AD dementia who meet the core clinical research criteria of the NIA-AA framework (McKhann, Knopman et al. 2011) The diagnostic criteria require that patients must exhibit impairments in both cognitive and functional domains for probable AD with documented evidence of progression of disease to be recruited.
INCLUSION CRITERIA	1. Male or female aged 60 - 85 years (inclusive). 2. Participant is an outpatient living at home or in an assisted living facility and is willing to attend all planned visits during the study. 3. The participant has a study partner (who is not expected to change during the study) who will accompany the patient to the clinic, and/or be available by telephone at designated times, monitor administration of prescribed medications, control the minimum 2-hour daily light exposure requirement. The study partner must, in the opinion of the investigator, have enough contact with the participant to be able to perform the duties described above. 4. Signed informed consent from the patient who has the capacity to provide informed consent as judged by the study investigator 5. Signed informed consent from the study partner. 6. Meets NIA-AA research criteria for probable AD (McKhann, Knopman et al. 2011). 7. Patient has a clearly documented history of cognitive decline over at least 12 months. 8. Patient has MRI / CT scan, performed within 12 months before Screening, with findings consistent with the diagnosis of AD without any other clinically significant comorbid pathologies as detailed in Appendix 3. If MRI/CT was not performed within 12 months before Screening, it can be done during the screening period (Table 10.1). . 9. MMSE score of 20 -- 26 (inclusive) at Screening and stability of MMSE – no more than a three point change on successive screening and baseline visits before randomization. 10. Patient has a CDR--GS of 0.5-or 1 (mild dementia) at Screening. 11. Patients taking acetylcholinesterase inhibitors and or memantine for the treatment of AD may be enrolled if the patient has been taking such medication for at least 6 months before Visit 2 (Baseline) and is stable on any dose for the last 4 months prior to Baseline, and if the dose is not expected to change during study participation.

	12. Patients not receiving acetylcholinesterase inhibitors may be enrolled but must be stable off acetylcholinesterase inhibitors for at least 3 months before Baseline, and agreeable to not starting throughout the first 26 weeks of the trial. 13. Patient has a negative drug screen (benzodiazepines or opiates) at Screening. Positive drug screen of BZDs, is allowed only if the use is intermittent and drug intake was 4 days or more before the visit (See Section 12.9.1). 14. Female patients must have had last natural menstruation ≥ 24 months before Screening OR be surgically sterile. 15. Male patients and their female spouse/partners who are of childbearing potential must agree to use highly effective methods of contraception, consisting of 2 forms of birth control (at least one of which must be a barrier method) starting at Screening, throughout the study and for 90 days post-last dose, OR be surgically sterile. 16. Patients who are taking medications for non-excluded concurrent medical conditions should be on a stable dose for at least 4 weeks before Screening. Patients taking allowed antidepressants (see Section 12.9) should be on a stable dose for at least 3 months before Screening and throughout the study. 17. Patient has ability and commitment to spend at least 2 hours per day exposed to daylight (preferably outside but can be next to a window if weather or personal situation does not permit). 18. Participant and study partner have the ability to read and write in English or Spanish and have hearing, vision, and physical abilities adequate to perform assessments (corrective aids allowed). 19. Participant and study partner are fully vaccinated for COVID 19 including booster doses as indicated (6 months post second dose). Having been diagnosed with COVID 19 after completing the initial full Covid vaccine would meet the requirements for a booster shot.
EXCLUSION CRITERIA	Potential patients who meet any of the following criteria will be excluded from participating in the study: 1. Declines whole genome screening for 2:107,510,000-107,540,000 polymorphism and APOE4 genotyping. 2. Patient is 2:107,510,000-107,540,000 polymorphism carrier. 3. Patient has an alternative cause for dementia other than AD. 4. A past or recent CT or MRI scan or report indicating any cortical infarct defined as > 1.5 cm^3; more than 2 lacunar infarcts defined as ≤ 1.5 cm^3; or diffuse white matter disease), Fazekas score of more than 1 on MRI or CT Scan (more details Appendix 3).

	5. Patient has evidence of any clinically significant neurodegenerative disease, or other serious neurological disorders other than AD as detailed in Appendix 3. 6. Patient has a concurrent psychiatric disorder that prevents his/her participation in the trial including but not limited to a lifetime diagnosis of Schizophrenia, Bipolar and related disorders, or Major Depressive Disorder, Substance and/or Alcohol use disorders within the past 2 years prior to Screening (See Appendix 3). 7. Patient has a history of uncontrolled or untreated cardiovascular, endocrine, gastrointestinal, respiratory, or rheumatologic disorders within the past 5 years. 8. Patients with a history of severe agitation within 12 months prior to Screening that requires (or has required) pharmacological treatment. 9. Patient has a history of serious infectious disease including: a) Neurosyphilis b) Meningitis c) Encephalitis 10. Patient has a history of a primary or recurrent malignant disease that has not been in remission for > 5 years prior to the Screening visit, with the exceptions of excised cutaneous squamous cell carcinoma in situ, basal cell carcinoma without recurrences; and history of intraductal breast cancer, cervical carcinoma in situ, or in situ prostate cancer resected over 5 years previously. (For resected in situ prostate cancer, i.e., high-grade intraepithelial neoplasia, the patient must have a normal prostate-specific antigen [PSA] prior to Screening and no increase in PSA since his resection surgery). 11. Patient has severe pain that is likely to interfere with sleep (in the opinion of the investigator). 12. Patient has any concomitant documented progressive disease likely to interfere with the conduct of the study, particularly: a) Liver disease with aspartate aminotransferase (AST), alanine aminotransferase (ALT) or gamma-glutamyltransferase (GGT) > 3 times the upper limits of normal (ULN) b) Total bilirubin > 3 times the ULN c) Mean corpuscular volume > 95 fl if due to chronic alcoholism d) Renal failure with creatinine clearance < 30 ml / min / 1.73m^2 13. Patients that are taking prohibited medications according to Appendix 2 see also section 12.9.

	14. Continuous use of benzodiazepines or other sedative-hypnotics during the 2 weeks before Screening (see Section 12.9). 15. Patient has a history of chronic use (more than 3 months of continuous use) and abuse of benzodiazepines or other sedative-hypnotics. 16. Use of any kind of melatonin/melatonin agonist during the 2 weeks before Screening (see Section 12.9). 17. Patient has known or suspected hypersensitivity to exogenous melatonin or melatonin receptor agonists. 18. Patient has clinically significant abnormal laboratory findings that have not been approved by the study Medical Monitor. 19. Patient has persistent bradycardia (heart beat < 50 bpm) or tachycardia (heart beat > 100 bpm) for the duration of the screening visit. 20. Patient has atrioventricular block (type II/Mobitz II and type III), congenital long QT syndrome, sinus node dysfunction or a marked prolongation of QTc interval (repeated demonstration in ECGs of QTc interval > 450 msec for males and > 470 msec for females using Fridericia's formula: QTc = QT/cube root of RR). 21. Patient has other serious diseases that could interfere with patient assessment, in the opinion of the investigator. 22. Patient has untreated B12 and/or folic acid deficiency. 23. Patient has participated in a clinical trial with any investigational agent within 3 months before Screening. Participants in any former monoclonal antibody clinical trial for AD are not eligible until 6 months after the last visit of the previous study. Patients who have received active vaccine for AD in the past will be excluded. 24. Patient with a body mass index (BMI) above 35 or below 18. 25. Lifestyle exclusions: a) Patients unwilling to limit alcohol intake to less than 30 g of pure alcohol per day (see Appendix 1) and to abstain after 2000h throughout the study b) Patients unwilling to be exposed to at least 2 hours of daylight each day c) Divergence from the accepted level of study medication compliance (70%-130% of expected consumption) as verified at Visit 2 (see Section 12.10) d) Patients consuming more than 7 cups of tea or coffee (or equivalent amount of caffeine [650 mg] in other caffeinated beverages) per day e) Patients with an irregular lifestyle or life pattern (eg, shift workers, patients likely to be jet lagged)

	26. Patients with evidence of serious risk of suicide based on the Columbia-Suicide Severity Rating Scale, i.e., active suicidal ideation with some intent to act, with or without a specific plan (a positive response to Suicidal Ideation Items 4 or 5) in the 6 months prior to Screening, **OR** with evidence of suicidal behavior in the 2 years prior to Screening (a positive response to any of the 5 Suicidal Behavior Items {actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior}), **OR** who, in the opinion of the investigator, present a serious risk of suicide.
EFFICACY PARAMETERS **Primary parameter**	- ADAS-cog14
Secondary parameters	- ADCS-iADL - MMSE - ADCS-CGIC - NPI - PSQI
Exploratory parameters	Disease modifying effects on - ADAS-cog14 - MMSE - ADCS-iADL - CDR-SB
SAFETY PARAMETERS	Vital signs measurements (heart rate and blood pressure), reported AEs or SAEs, physical examinations, clinical laboratory evaluations (hematology, biochemistry, and urinalysis), 12-lead ECGs, C-SSRS
PRIMARY EFFICACY STATISTICAL ANALYSIS	The primary efficacy analysis for change from baseline in ADAS-cog14 score will be carried out using an analysis of covariance (ANCOVA) model with treatment as the main effects, and baseline ADAS-cog14 and APOE genotype, as a covariates. The primary timepoint is after 26 weeks of double-blind treatment.
SECONDARY EFFICACY STATISTICAL ANALYSIS	The ADAS-cog14 and all secondary efficacy parameters: ADCS-iADL, ADCS-CGIC, MMSE, NPI and PSQI, will be summarized at baseline, after 13, and after 26 weeks of double-blind treatment and after 39, 52 and 78 weeks after randomization in the extension period (actual and change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). MMRM model will be used to analyze ADAS-Cog14 and all secondary efficacy endpoints: ADCS-iADL, ADCS-CGIC, MMSE, NPI and PSQI, utilizing all baseline and postbaseline data

	during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. The treatment difference estimates at each visit will be reported, with 95% confidence intervals and P values. For the primary parameter ADAS-cog14 and key efficacy parameter ADCS-iADL, the multiple imputation may be used for dealing with missing data. The ANCOVA model will also be used to analyze these secondary efficacy endpoints
EXPLORATORY EFFICACY STATISTICAL ANALYSIS	The following exploratory efficacy parameters will be summarized descriptively: 1 .Long-term safety and efficacy of 18 months piromelatine 20 mg compared to end of the double-blind period . 2 .Disease modifying potential comparing a) Difference from baseline in mean ADAS-cog14 scores in the early and delayed start groups by 52 and 78 weeks of treatment. b) Difference from baseline in mean MMSE, CDR-SB scores in the early and delayed start groups by 78 weeks of treatment. c) Rate of progression in the 26 weeks extension period and the first 26 weeks randomized period for each group (ADAS-cog14, MMSE, ADCS-iADL).
SAFETY ANALYSIS	Descriptive statistics will be provided for AEs, physical examination, change in laboratory parameters, vital signs and ECG. The number of patients taking concomitant medications during the 28-week treatment period (2-week single-blind placebo run-in period followed by 26-week double-blind treatment period) and end of 78 weeks treatment period (single blind treatment) will be summarized by WHO drug classification code for each treatment group. The number of patients withdrawing during the treatment periods will be summarized by primary reason for withdrawal for each treatment group. The number of patients reporting AEs will be summarized during the 28-week treatment period by system organ class and preferred term for each treatment group. The change in laboratory parameters from baseline (end of the first week) to the end of the 28-week treatment period and end of 78 weeks treatment period will be summarized descriptively. The shift tables will also be used showing the number of patients having values below, within, and above the normal range at each assessment for each treatment group separately. Data will not be carried forward for patients withdrawing due to treatment failure. Physical examination parameters will be summarized as the number of patients who have a normal or abnormal examination at each

	assessment for each treatment group separately. Data will not be carried forward for patients withdrawing due to treatment failure. Vital signs and ECG will be summarized at baseline and at the end of the 28-week treatment period (actual and change from baseline) using descriptive statistics (n, mean, SD, median, minimum, and maximum). The number of patients withdrawing during the 28-week treatment period and end of 78 weeks treatment period will be summarized by primary reason for withdrawal for each treatment group. No formal statistical testing will be performed on the safety data. These safety parameters will be assessed using the safety analysis set.	
PLANNED TRIAL DATES	First patient in: May 2022	Last patient out: May 2025

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5. ETHICS

5.1 REGULATORY AND ETHICAL APPROVALS

The regulatory permission to perform the study will be obtained in accordance with applicable regulatory requirements. The institutional review board (IRB) will approve this protocol, the patient informed consent form (ICF), the informant ICF, and their updates. The regulatory and ethical approvals must be available before a patient is exposed to any study-related procedure, including screening tests to determine eligibility for the study.

5.2 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the following:

- Principles of the Declaration of Helsinki (revised version of Seoul, Korea, October of 2008).
- Good Clinical Practice (GCP) guidelines, as defined by The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Tripartite Guideline for Good Clinical Practice: E6(R1) (ICH E6), the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) – Protection of Human Subjects and Part 56 (21CFR56) – IRBs.
- IRBs, Health Insurance Portability and Accountability Act (HIPAA), and all other applicable local regulatory requirements and laws.

5.3 PATIENT INFORMATION AND CONSENT

The investigator will obtain a freely given written consent from each patient and informant after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study that is relevant to his/her decision to participate. The patient must be capable to sign the consent form as judged by the study investigator and as dictated by local legal circumstances. The consent form will be signed and dated by the patient/informant before he/she is exposed to any study-related procedure, including screening tests for eligibility. Each patient will authorize in writing that his/her source records may be reviewed by a monitor, an auditor, or a regulatory inspector, in accordance with applicable regulatory requirements. Patients will sign a separate applicable ICF for the apolipoprotein-E (ApoE4) and 2:107,510,000-107,540,000 polymorphism genotyping.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be a multicenter study conducted in the North America (NA) and Europe (EU).

Study CRO

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7. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATIONS

21CFR11	United States Code of Federal Regulations, Title 21, Part 11 – Electronic records and electronic signatures
21CFR50	United States Code of Federal Regulations, Title 21, Part 50 – Protection of Human Subjects
21CFR56	United States Code of Federal Regulations, Title 21, Part 56 – IRBs
Aβ	β-amyloid peptide
AD	Alzheimer's disease
ADAS-cog14	Alzheimer's Disease Assessment Scale – cognitive subscale (also related: ADAS-cog13, ADAS-cog12, and ADAS-cog11)
ADCOMS	AD Composite Score
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living
ADCS-iADL	Alzheimer's Disease Cooperative Study - Instrumental Activities of Daily Living
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APOE4	apolipoprotein-E (gene)
AST	aspartate aminotransferase
BMI	body mass index
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating Global Score
CDR-SB	Clinical Dementia Rating Sum of Boxes
CFT	Categorical Fluency Test
ADCS-CGIC	Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change
cNTB	Computerized Neuropsychological Test Battery
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
ECG	electrocardiogram
eCRF	electronic case report form
EEG	Electroencephalogram

EU	Europe
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonization
ICH E3	International Conference on Harmonization Tripartite Guideline E3: Structure and Content of Clinical Study Reports
ICH E6	International Conference on Harmonization Tripartite Guideline E6(R1): Good Clinical Practice
IRB	institutional review board
IWRS	interactive web response system
MCI	mild cognitive impairment
MMRM	mixed-effects maximum likelihood repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NA	North America
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI	Neuropsychiatric Inventory
NREM	non-rapid eye movement
NTB	Neuropsychological Test Battery
PET	positron emission tomography
PK	pharmacokinetic(s)
PSA	prostate-specific antigen
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
SWS	slow wave sleep
ULN	upper limits of normal
US	United States
WASO	wake after sleep onset

DEFINITION OF TERMS

Safety analysis set	All patients randomized to treatment who have taken at least 1 dose of study medication
Full analysis set	All patients in the safety analysis set who satisfy all entry criteria and who have efficacy data for the primary parameter recorded for baseline and at least 1 post baseline period assessment
Per protocol set	All patients in the full analysis set who have no major protocol violations

8. INTRODUCTION

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the leading cause of dementia in the elderly population. . Effective treatments for the devastating disease are urgently needed as the world's population continues to age.

The diagnosis of AD is generally based on consensus diagnostic criteria developed by the National Institute on Aging-Alzheimer's Association (NIA-AA) (McKhann, Knopman et al. 2011). These criteria are clinical in nature and require that patients must exhibit impairments in both cognitive and functional domains. In the earliest clinical stages of AD, subtle cognitive deficits may be evident only through use of sensitive measures of neuropsychological performance. Thereafter, but before developing overt dementia, patients proceed through a clinical phase where cognition becomes increasingly affected and relatively mild but detectable impairments in some functional abilities emerge as well.

The presence of extracellular β-amyloid deposition as neuritic plaques and intracellular accumulation of hyperphosphorylated tau as neurofibrillary tangles remains the primary neuropathologic criteria for AD diagnosis(Long and Holtzman 2019). However, numerous phase 3 clinical trials, aimed at the abnormal production and aggregation of Aβ have failed to improve neuropsychological performance and functional abilities, and slow down disease progression.

Piromelatine

The investigational compound, N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-4-oxo-4H-pyran-2-carboxamide (piromelatine) is a novel melatonin MT1, 2, and 3 and serotonin 5-HT-1A and -1D receptors agonist with a different proposed mechanism of action than currently available AD medications. Simultaneous activation of melatonergic and 5HT-1a receptors may synergistically promote neurogenesis (Fava, Targum et al. 2012). Melatonin receptor agonism, which maintains the NREM SWS (Arbon, Knurowska et al. 2015), appears beneficial for cognition and functioning in mild to moderate AD patients (Wade, Farmer et al. 2014). Through this unique molecular mode of action, piromelatine demonstrated in preclinical studies in rodents neuroprotective (Tang, Wang et al. 2012, Buendia, Navarro et al. 2014), memory enhancing (Tian, Laudon et al. 2010, He, Ouyang et al. 2013), sleep promoting (Liu, Yin et al. 2014), and neurogeneration enhancing capabilities (Tian et al., 2015 unpublished) with relevance to AD risk factors, comorbidities, and symptoms.

Clinical Studies

In a Phase 1 study in healthy volunteers, piromelatine (2, 5, 20, 50, and 200 mg) was found to be safe and well tolerated with no serious adverse events (SAEs) and showed a favorable, dose-proportional pharmacokinetic (PK) profile following oral intake. In addition, piromelatine intake was associated with increase in fatigue and total sleep time in the volunteers in a dose-dependent manner (Yalkinoglu, Zisapel et al. 2010). In a Phase 1b multiple ascending dose study in insomnia patients, piromelatine (2, 5, 20, and 50 mg) had a favorable PK profile without any sign of accumulation. Importantly, in this study piromelatine administered for 5 days to nondemented patients with insomnia had no detrimental nor beneficial effect on learning and memory as measured using the word-pair association task (Laudon, Katz et al. 2012).

In a Phase 2, randomized, placebo-controlled, sleep laboratory study in insomnia patients (n=137 aged 18-80), piromelatine (20 mg and 50 mg daily for 1 month) enhanced sleep maintenance (wake after sleep onset [WASO]) measured by polysomnography (PSG) significantly in comparison to placebo (Neurim press release, 2013).`. Overall, piromelatine was generally safe and well tolerated. There were no SAEs during the conduct of this study. Adverse event (AE) rates during double-blind treatment with study medication were low (6.7% in the piromelatine 20 mg group, 0% in the piromelatine 50 mg and placebo groups). Laboratory values were within normal ranges. No clinically meaningful changes in vital signs, electrocardiograms (ECGs), or physical examinations were observed. No suicidal behavior

or suicidal ideation (Columbia Suicide Severity Rating Scale [CSSRS]) was recorded at any time during the study.

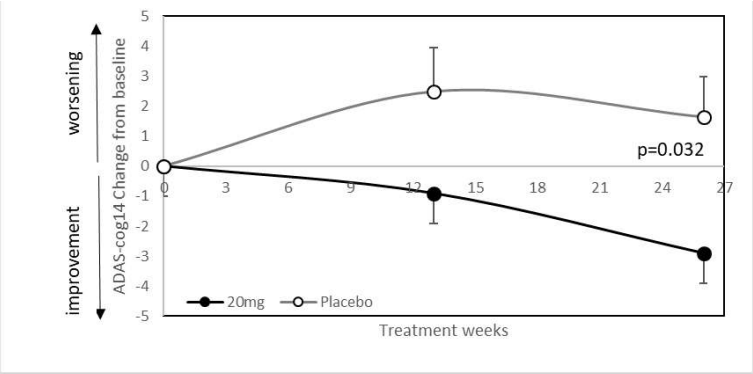
In a Phase 2, randomized, placebo-controlled, dose-ranging study of piromelatine (5, 20, and 50 mg daily for 6 months) in patients with mild dementia due to Alzheimer's disease (n=352 age 60-85 years) (ReCognition study) there were no safety concerns in this study, and no specific trends in adverse events (AEs) by treatment group or piromelatine dose were noted. The incidence of the treatment emerging adverse events (TEAEs) observed in the placebo group (48.6%) was similar to the incidence observed in the piromelatine groups (44.3% in the 5-mg group, 56.8% in the 20-mg group, and 39.1% in the 50-mg group). The most frequently reported TEAE was headache in 19 patients (5.2%) with 34 events in total, followed by nasopharyngitis in 18 patients (4.9%) with 20 events. No statistically significant differences in the changes from baseline were observed in the primary endpoint (the global composite score of the computerized Neuropsychological Test Battery (cNTB)), secondary or exploratory endpoints between the placebo and piromelatine groups. These included, Clinical Global Impression of Change (CGIC), Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) patients (ADCS-MCI-ADL), Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog14) or Pittsburgh sleep quality index (PSQI)).

Genome wide association study (GWAS)

A Genome wide association study (GWAS) of a representative sample (N=107) of the ReCognition cohort identified an association between response to piromelatine (enhancement in cognitive functioning as assessed by cNTB) and the presence of 5 to 6 single nucleotide polymorphisms in chromosome 2, 2:107,510,000-107,540,000 locus ((as disclosed in the Genome Reference Consortium Human genome build 37 (GRCh37)) referred to as 2:107,510,000-107,540,000 polymorphism). This genetic marker, reportedly present in ca. 17% of the global population (www.niagads.org/genomics/), was present in 27% of participants with mild dementia due to Alzheimer's disease in the ReCognition study. In a subsequent post hoc analysis, it was found that the participants with 2:107,510,000-107,540,000 polymorphism had significant worsening on ADAS-Cog14 and PSQI with piromelatine 20 mg compared to placebo. There was no interaction with APOE4 genotype. The worsening in ADAS-Cog14 in participants with 2:107,510,000-107,540,000 polymorphism was significantly correlated with the worsening in PSQI (R=0.56; p=0.029). Deterioration in cognition from healthy controls through MCI to AD patients was associated with parallel deterioration in sleep had been documented (Economou, Papageorgiou et al. 2013). Sedative hypnotic drugs, e.g. benzodiazepines may have alerting effects in some subjects (Mancuso, Tanzi et al. 2004, Akeju and Brown 2013, Jordahn, Andersen et al. 2016). Accordingly, the worsening in ADAS-Cog14 in participants with 2:107,510,000-107,540,000 polymorphism may be linked to an unwanted increase in alertness with piromelatine. This worsening calls for exclusion of 2:107,510,000-107,540,000 polymorphism carriers from future studies of piromelatine in mild dementia due to Alzheimer's Disease.

In contrast, in 2:107,510,000-107,540,000 polymorphism non-carriers, piromelatine 20 mg, improved ADAS-cog14 (effect sizes 0.72) compared to placebo. PSQI also improved significantly with piromelatine 20 mg compared to placebo (effect sizes 0.63). Considerable effects size (0.26 and 0.38) were also found for ADCS-ADL and ADCS-CGIC. The 20 mg dose evoked the full response. The response appeared to increase with time (Figure 1). The improvement in ADAS-Cog14 in 2:107,510,000-107,540,000 polymorphism non-carriers was independent of the improvement in sleep or baseline PSQI levels. There was no interaction with APOE4 genotype [Schneider et al, A Polymorphism Cluster at the 2q12 locus May Predict Response to Piromelatine in Patients with Mild Alzheimer's Disease, JPAD 2021 (accepted for publication)].

Figure 1: Effects of piromelatine 20 mg and placebo treatment on ADAS-cog14 scores (ReCognition study) in patients with mild dementia due to Alzheimer's disease who are 2:107,510,000-107,540,000 polymorphism non-carriers (n=23,19 for piromelatine and placebo groups respectively)



Proposed Trial

Based on the above, this study of piromelatine in participants with mild dementia due to Alzheimer's disease is conducted as a confirmatory, randomized efficacy and safety study of 20 mg piromelatine versus placebo on cognitive decline in participants who are 2:107,510,000-107,540,000 polymorphism non-carriers (N=225).

To evaluate the potential disease modifying effects of piromelatine, completers will be offered to enter into a 12 months extension phase of piromelatine 20 mg daily (Delayed start design (Verschuur, Suwijn et al. 2015)). This exploratory phase will serve to follow up on the long term (18 months) efficacy and safety of the test drug in the Early group and to evaluate the potential disease modifying effect by comparing the effects in Delayed group placebo randomized participants who started the treatment with a 26 weeks delay

An interim efficacy analysis (blinded) is intended after completion of the 26 weeks double blind period; if efficacy is not confirmed, the study will be terminated without completing the extension period.

A computer generated randomization schedule (1:1 piromelatine:placebo) will include stratification for APOE4 carriers measured by the Precivity test in the piromelatine and placebo arms.

9. OBJECTIVES OF THE STUDY

9.1 PRIMARY OBJECTIVE

To compare the effect of piromelatine (20 mg) to that of placebo on the ADAS-cog14 at Week 26 of double-blind treatment.

9.2 SECONDARY OBJECTIVES

9.2.1 Key Secondary Objective

To compare the effect of piromelatine (20 mg) to that of placebo on ADCS-iADL at Week 26 of double-blind treatment

9.2.2 Secondary Objective

1. To compare the effect of piromelatine (20 mg) to that of placebo on global impression assessed by the ADCS-CGIC at Week 26 of double-blind treatment
2. To compare the effect of piromelatine (20 mg) to that of placebo on cognitive aspects of mental function assessed by MMSE at Week 26 of the double-blind treatment

3. To compare the safety and tolerability of piromelatine (20 mg) to that of placebo over 26 weeks of double-blind treatment.

9.2.3 Other Secondary Objectives

4. To compare the effect of piromelatine (20 mg) to that of placebo on behavioral igns and symptoms assessed by the NPI scale after 26 weeks of double-blind treatment

5. To compare the effect of piromelatine (20 mg) to that of placebo on PSQI at Weeks 13, and 26 and over 26 weeks of double-blind treatment

9.2.4 Exploratory Objectives

1. Long term safety and efficacy of 18 months piromelatine 20 mg compared to end of the double-blind period.

2. Disease modifying potential comparing mean difference from baseline in ADAS-cog14, MMSE, CDR_SB scores in the early and delayed start groups by 78 weeks of treatment and the differences in the means between the groups. Rate of progression in the 26 weeks extension period and the first 26 weeks randomized period for each group (ADAS-cog14, MMSE, ADCS-iADL).

10. INVESTIGATIONAL PLAN

10.1 OVERALL STUDY DESIGN AND PLAN

This study in participants with mild dementia due to Alzheimer's disease is conducted as a confirmatory, randomized efficacy and safety study of 20 mg piromelatine versus placebo in participants who are 2:107,510,000-107,540,000 polymorphism non-carriers and as an exploratory study of potential disease modifying effects of the drug. Following informed consent, patients with a documented history of mild dementia due to AD for at least 12 months, having an MMSE score of 20 to 26 (inclusive) at Screening, and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1 will be recruited and further screened for eligibility. Informant commitment for the study is also necessary (defined as someone who is not expected to change during the course of the study and is responsible for the overall care of the patient at home).

At Screening (Visit 1), patients will undergo neuropsychiatric assessments, psychometric testing, and general medical assessments (including medical history, pre-existing conditions, physical examination, vital signs, and ECG). If patients have not had brain imaging with findings consistent with the diagnosis of dementia due to AD in the last 12 months, a computed tomography (CT) or magnetic resonance imaging (MRI) scan will be obtained to rule out clinically significant comorbid pathologies. A whole genome sequencing will be obtained for 2:107,510,000-107,540,000 polymorphism. In addition, plasma biomarkers assessment will be done using the high amyloid probability score (APS) by the PrecivityAD™-Aβ blood test which will also provide APOE3/4 and pTau 181/217 presence in plasma. Rescreening will be allowed on specific cases following a decision by the medical monitor.

Potentially eligible patients will be given a bottle of run-in placebo (single blind) with instructions not to begin taking the doses until they receive a phone call from the site staff. Site staff will send MMSE, Clinical Dementia Rating (CDR), ADAS-cog, gene screen results and documented history of cognitive deterioration of these potential eligible patients who are 2:107,510,000-107,540,000 polymorphism non-carriers to be centrally reviewed. After confirmation of eligibility from the Clinical Surveillance & Training team (CST) and up to 4 weeks after screening visit, eligible patients will start a 2-week run-in period of placebo (single blind), followed by 26 weeks of double-blind treatment comprising administration of piromelatine or placebo, for a total treatment duration of 28 weeks. During the double-blind period, patients will be enrolled in a 1:1 randomization ratio to 2 trial arms (placebo and piromelatine 20 mg). Because of expected faster deterioration, APOE4 carriers will be stratified between the randomization groups. Additional patient eligibility procedures and information is outlined in section 11.1.4.

Intermediate visits in the double-blind phase will be carried out at 13 weeks (Visit 3) and 26 weeks (Visit 4) after randomization.

An efficacy analysis (blinded) is intended after completion of the 26 weeks double blind period; if efficacy is not confirmed, the study will be terminated without completing the extension period. If efficacy is confirmed the study will be extended, the assignments of the patients during the double-blind phase will be maintained blinded until end of the extension phase to allow evaluation of the potential disease modifying effects.

There are 3 assessments in the extension period for the 2:107,510,000-107,540,000 polymorphism non-carriers: at 39 (Visit 5), 52 (Visit 6) and 78 weeks (Visit 7) after

randomization. A follow-up phone call to elicit any safety concerns will be completed 2 weeks after the last dose of study medication. Patients who discontinue prior to Visit 4 (Week 26) will be brought back for a termination visit as soon as possible after termination and not later than week 26.

Piromelatine (20 mg mg tablets) and placebo will be administered orally, once daily after a meal, before habitual bedtime, preferably between 2100h and 2300h. Patients will be required to spend at least 2 hours a day exposed to daylight.

Overall study design is shown in Figure 10.1.

Figure 10.1: Overall Study Design

	Screening / Single -Blind Run--in		**Randomization**	**Double-Blind placebo-controlled Treatment**		**Open-label extension (delayed start)**			
Period	**Screening**	**Run--in**	**Randomization**						**Follow--up Phone call**
Week	- 6	- 2	0	13	26	39	52	78	80
Visit	1		2	3	4	5	6	7	
Treatment	4 w no treatment+ 2 w Placebo			Piromelatine 20 mg or Placebo		Piromelatine 20 mg			N/A

The Schedule of Assessments is presented in Table 10.1.

Table 10.1: Schedule of Assessments

Period	**Screening/ Single-Blind Run-in[1]**	**Randomization**	**Double-Blind placebo-controlled Treatment**		**Open-label extension (delayed start)**			**Follow-up [a]**	**Premature Discontinuation Visit**
Visit	**1 [b]**	**2**	**3**	**4**	**5**	**6**	**7**		
Study Day	**–42 ±5[2]**	**0 ±5[2]**	**91 ± 5[2]**	**182 ± 5[2]**	**273±5[2]**	**364±5[2]**	**546±5[2]**	**560**	
Study Week		**0**	**13**	**26**	**39**	**52**	**78**	**80**	
Explanation of the study	X								
Informed consent - patient	X								
Informed consent - informant	X								
Screening number assigned	X								
Demographic data	X								
Medical and surgical history	X								
CT/MRI [c]	X								
PET/CSF data collection [d]	X								
Inclusion and exclusion criteria	X	X							
Randomization		X							

Period	**Screening/ Single-Blind Run-in[1]**	**Randomization**	**Double-Blind placebo-controlled Treatment**		**Open-label extension (delayed start)**			**Follow-up [a]**	**Premature Discontinuation Visit**
Visit	**1 [b]**	**2**	**3**	**4**	**5**	**6**	**7**		
Study Day	**–42 ±5[2]**	**0 ±5[2]**	**91 ± 5[2]**	**182 ± 5[2]**	**273±5[2]**	**364±5[2]**	**546±5[2]**	**560**	
Study Week		**0**	**13**	**26**	**39**	**52**	**78**	**80**	
Physical examination	X		X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	X		X
BMI	X			X			X		
Concomitant medications	X	X	X	X	X	X	X		X
12-lead ECG	X			X			X		X
Hematology/biochemistry/ urinalysis[e]	X		X	X[m]			X		X
Hormonal testing	X			X			X		X
Precivity test[f]	X						X		
Blood sampling for 2:107,510,000-107,540,000 polymorphism [g h]	X								
Urine drug screen (BZDs and opiates)	X		X		X				
Recording of adverse events		X	X	X	X	X	X	X	X
C-SSRS	X		X	X	X	X	X		X
Compliance verification		X	X	X	X	X	X		
Precivity and 2:107,510,000-107,540,000 polymorphism review		X							
MMSE	X	X		X			X		
ADAS-cog14	X [i]	X	X	X	X	X	X		X
ADCS-CGIC		X	X	X			X		
ADCS-ADL		X	X	X	X	X	X		X
CDR	X	X		X			X		
NPI		X		X			X		
PSQI		X	X	X	X	X	X		
CST Eligibility Review[L]	X								
Study medication dispensed	X[n]	X	X	X	X	X			
Collection of unused study medication and used packs since last visit		X	X	X	X	X	X		X
Run-in phone call [j]	X								

Period	Screening/ Single-Blind Run-in[1]	Randomization	Double-Blind placebo-controlled Treatment		Open-label extension (delayed start)			Follow-up [a]	Premature Discontinuation Visit
Visit	**1** [b]	**2**	**3**	**4**	**5**	**6**	**7**		
Study Day	**–42 ±5**[2]	**0 ±5**[2]	**91 ± 5**[2]	**182 ± 5**[2]	**273±5**[2]	**364±5**[2]	**546±5**[2]	**560**	
Study Week		**0**	**13**	**26**	**39**	**52**	**78**	**80**	
Compliance phone call [k]	On Days (±3) (every week between Visits 2-4 and every 2 weeks (±5) between visits 5-7) [j] Days 7 ± 3, 14 ± 3, 21 ±3, 28±3, 35 ± 3, 42 ± 3, 49 ± 3, 56 ± 3, 63 ± 3, 70 ± 3, 77 ± 3, 84 ± 3, 98 ± 5, 105 ± 5, 112 ± 5, 119 ± 5, 126 ± 5, 133 ± 5, 140 ± 5, 147 ± 5, 154 ± 5, 161 ± 5, 168 ± 5, 175 ± 5, 196 ± 5, 210±5, 224 ± 5, 238 ± 5 , 252 ± 5, 287 ± 5, 301 ± 5, 315 ± 5, 329 ± 5, 343 ± 5 ,357 ± 5, 378 ± 5, 392 ± 5, 406 ± 5, 420 ± 5, 434 ± 5, 448 ± 5, 462 ± 5, 476 ± 5,490 ± 5, 504±5, 518±5 and 532±5.								

Key: ADAS-cog14 = Alzheimer's Disease Assessment Scale (cognitive subscale); ADCS-ADL = Alzheimer's Disease Cooperative Study - Activities of Daily Living; ApoE4 = apolipoprotein-E (gene); BMI = body mass index; BZD = benzodiazepine; CDR = Clinical Dementia Rating; ~~CFT = Categorical Fluency Test;~~ ADCS-CGIC = Alzheimer's Disease Cooperative Study -Clinical Global Impression of Change; CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; PSQI = Pittsburgh Sleep Quality Index; C-SSRS - Columbia Suicide Severity Rating Scale.

[1] Placebo run in treatment period is 14 days +/- 5 days

[2] This visit window may be extended due to extenuating circumstances with the approval of the Medical Director and the sponsor. If the subject is granted an extension subject should continue dosing until the next visit. There should be no break of study medication.

[a] The Follow-up visit consists of a phone call to the informant to elicit any safety concerns 2 weeks after the last dose of study medication.

[b] Visit 1 may be completed over 2 consecutive days (no Friday/Monday visits) at the discretion of the investigator. Both the patient and informant must be present both days, and the following screening procedures should be completed on the indicated day: Screening Day 1: MMSE, ADAS-cog,; Screening Day 2: CDR, C-SSRS.

[c] Only if a CT or MRI scan was not performed in the past or if available scan with findings consistent with the diagnosis of dementia due to AD without any other clinically significant comorbid pathologies was performed more than 12 months before Screening. The scan should be performed, and diagnosis confirmed prior to Visit 2.

[d] Only for patients who have this information available.

[e] It is recommended that blood samples should be drawn in the morning. If the blood sample at Visit 1 is drawn in the afternoon, then next visits sample should also be drawn in the afternoon.

[f] Precivity test at screening visit and at visit 7 Tau 181 / 217

[g] If whole genome sequencing was not performed in the past the analysis should be performed and exclusion of 2:107,510,000-107,540,000 polymorphism carriers and non-carriers confirmed prior to Visit 2.

[h] Retrospective genetic information could be used.

[i] Practice session

[j] On Day –14, after eligibility review by Clinical Surveillance & Training team (CST).

[k] The informant will be called by study personnel for follow-up and safety and compliance verification purposes (eg, study medication compliance, daylight exposure compliance, and adverse event/concomitant medication checks).

[L] Eligibility Review packet will be submitted for review to the Clinical Surveillance & Training (CST) team as soon as the diagnostic process and the screening assessments are completed (refer to section 11.1.4)

[m] B^{12} test only at Visit 4

[n] The drug can be dispensed at any point in the screening period or once eligibility is confirmed

10.2 DISCUSSION OF STUDY DESIGN

Piromelatine proposed mode of action and previous studies suggest that this molecule may improve cognitive performance via its neuroprotective effects and activity in circadian rhythms and sleep pathways. Dose dependent sleep effects were demonstrated after 4 weeks of treatment in a Phase 2 sleep laboratory study with the 20 mg dose providing maximal effect for the elderly patients. Effects on cognition (ADAS-Cog 14 and 11) were seen in a phase 2 clinical study after 26 weeks of piromelatine 20 and 50 mg treatment in patients with mild dementia due to Alzheimer's disease who are 2:107,510,000-107,540,000 polymorphism non-carriers, with the 20 mg dose providing maximal effect.

The cognitive outcome measure mostly used in AD clinical trials, the ADAS-cog14, is a scale based on a series of items that assess different aspects of cognitive function known to be relevant to the cognitive dysfunction that characterizes AD (Greenberg, Carrillo et al. 2013).

Dosage specification was made on the basis of the previous studies showing that the 20 mg was the most effective dose for both insomnia and Alzheimer patients.

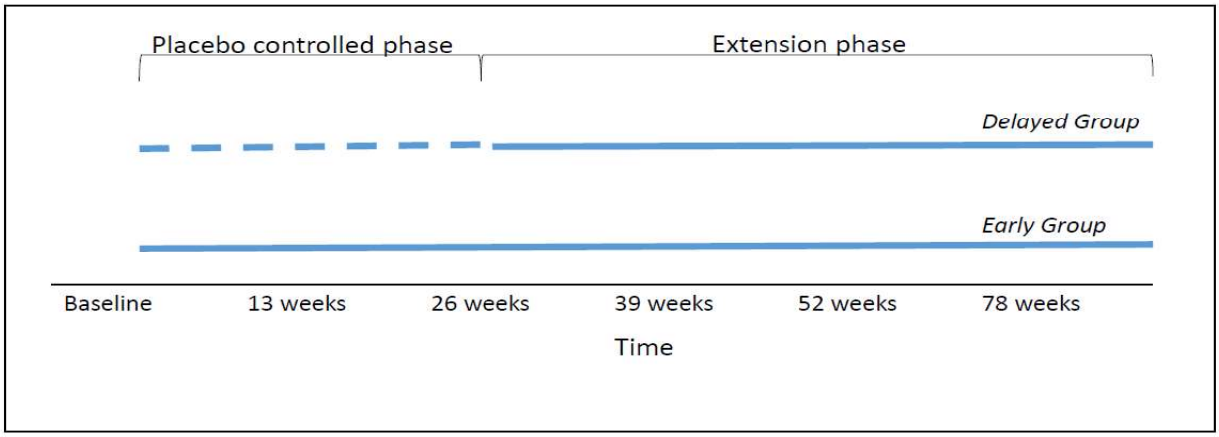
The parallel dosing regimen maximizes the ability to make direct comparison between the active treatment s and placebo group.

The use of placebo allows for a blinded, thus minimally biased, study. The placebo group is a comparator group for efficacy and safety assessment. The blinding will stay throughout the study into the extension phase to allow evaluation of potential disease modifying effects of the test drug.

Within -subject variation in psychometric test scores is common in AD patients. This could be the result of measurement error or reflection of the fluctuation in the patient's condition. Both cases may influence the final score. The first problem of rater errors will be addressed by employing strict rater training and by vigorous real-time monitoring of rater performances. In addition, in order to avoid habituation problems, all patients will receive a practice ADAS-cog14 assessment prior to their baseline measurements.

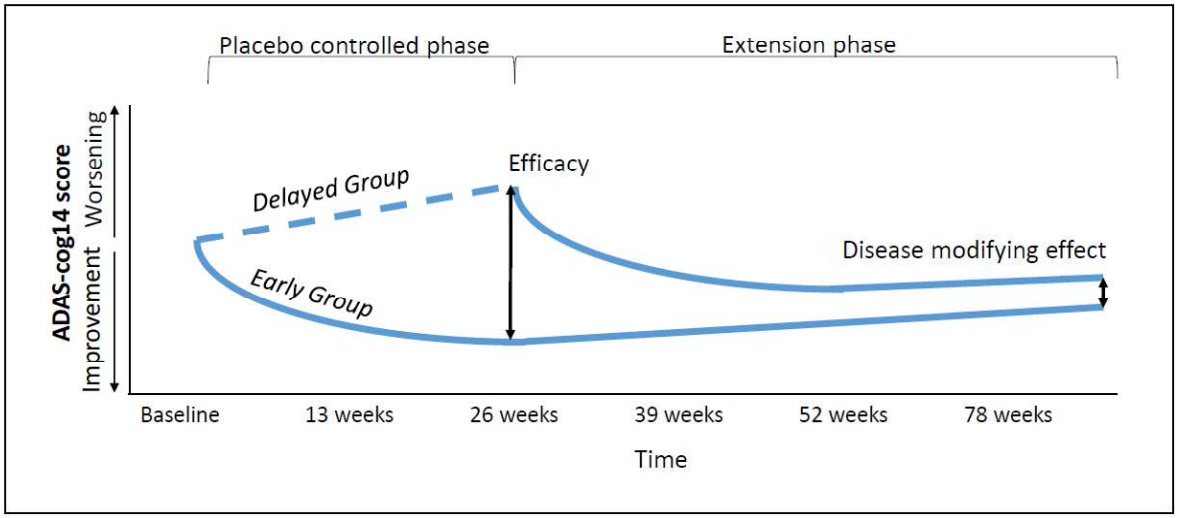
To evaluate the potential disease modifying effects of piromelatine, completers will be offered to enter into a 12 months extension phase of piromelatine 20 mg daily (Delayed start design (Verschuur, Suwijn et al. 2015)). This exploratory phase will serve to follow up on the long term (18 months) efficacy and safety of the test drug in the Early start group and to evaluate the potential disease modifying effect by comparing the effects in Delayed start group (placebo randomized participants) who started the treatment with 26 weeks delay (Figure 2).

Figure 2: Delayed-start design. Studies with a delayed-start design investigate two agents: active treatment (solid line) and control treatment (dashed line). In the placebo-controlled phase, patients are randomized to either active (piromelatine) or controlled (placebo) treatment. In the extension phase, both groups receive active treatment



The placebo-controlled phase of 26 weeks was chosen based on the results of the ReCognition study, which suggested symptomatic efficacy of piromelatine in subjects who are 2:107,510,000-107,540,000 polymorphism non-carriers after 26 weeks of treatment.
Ideally, the placebo-controlled phase of 26 weeks would even be longer because if a disease modifying effect exists, there would then be more time for the slopes of the two treatment groups to diverge further (Fig. 3). However, because of symptom progression, a placebo-controlled phase of more than 26 weeks would result in the retention of progressively fewer patients in the placebo-controlled phase of the study, making the placebo-controlled phase only slightly longer because of the increasing lower numbers in the delayed start group – thereby diminishing the theoretical advantage of a longer placebo-controlled phase. More importantly, poorer retention in the delayed-start group would compromise the ability to show a difference between the two groups and would potentially selecting outpatients with a milder or more slowly progressive disease course, thereby diminishing a possible existing difference between the two groups. The fact that all patients will subsequently get the test drug will also enhance recruitment and retention in the study through the placebo period.

Figure 3 Delayed-start design with beneficial effect of early treatment with piromelatine. If a beneficial disease modifying effect of piromelatine exists, patients in the early-start group will perform better at the end of the study than patients in the delayed-start group if the placebo- controlled phase is sufficiently long and if the beneficial disease modifying effect is maintained during the extension phase.



An efficacy analysis (blinded) is intended after completion of the 26 weeks double blind period; if efficacy is not confirmed, the study will be terminated without completing the extension period. If extended, the double blind assignment of the patients will be maintained until end of the extension phase to allow evaluation of the potential disease modifying effects.

10.3. SAFETY MONITORING

The sponsor (Neurim Pharmaceuticals [1991] Ltd) and the medical monitor will review safety data on an ongoing basis.

11. METHODOLOGY

11.1 SELECTION OF STUDY POPULATION

11.1.1 Number of Patients Screened, Entered and Completing

Male and female patients between the ages of 60 and 85 (inclusive) with mild AD will be screened for the study after having given their written informed consent. After 4-week screening period with no treatment and 2-week single-blind, placebo run-in period, at Visit 2, eligible patients who are non-carriers of 2:107,510,000-107,540,000 locus polymorphism will be randomized and treated with piromelatine (20 mg) or placebo as a double-blind treatment for 26 weeks. Assuming a 25% screen failure rate, 25% 2:107,510,000-107,540,000 polymorphism and allowing for 26% patient withdrawal, 400 patients should be screened in order to randomly assign 225 2:107,510,000-107,540,000 polymorphism non-carriers, of whom it is expected 166 will complete the 26 weeks study.

11.1.2 Inclusion Criteria

1. Male or female aged 60-85 years (inclusive).
2. Participant is an outpatient living at home or in an assisted living facility and is willing to attend all planned visits during the study.
3. The participant has a study partner (who is not expected to change during the study) who will accompany the patient to the clinic, and/or be available by telephone at designated times, monitor administration of prescribed medications, control the minimum 2-hour daily light exposure requirement. The study partner must, in the opinion of the investigator, have enough contact with the participant to be able to perform the duties described above.
4. Signed informed consent from the patient who has the capacity to provide informed consent as judged by the study investigator
5. Signed informed consent from the study partner.
6. Meets NIA-AA research criteria for probable AD (McKhann, Knopman et al. 2011).
7. Patient has a clearly documented history of cognitive decline over at least 12 months.
8. Patient has MRI/CT scan, performed within 12 months before Screening, with findings consistent with the diagnosis of AD without any other clinically significant comorbid pathologies as detailed in Appendix 3. If MRI/CT was not performed within 12 months before screening, it can be done during the screening period (Table 10.1).
9. MMSE score of 20-26 (inclusive) at Screening and stability of MMSE – no more than three-point change on successive screening and baseline visits before randomization.
10. Patient has a CDR-GS of 0.5 or 1 (mild dementia) at Screening.
11. Patients taking acetylcholinesterase inhibitors and or memantine for the treatment of AD may be enrolled if the patient has been taking such medication for at least 6 months before Visit 2 (Baseline) and is stable on any dose for the last 4 months prior to Baseline, and if the dose is not expected to change during study participation.

12. Patients not receiving acetylcholinesterase inhibitors may be enrolled but must be stable off acetylcholinesterase inhibitors for at least 3 months before Baseline, and agreeable to not starting throughout the first 26 weeks of the trial.
13. Patient has a negative drug screen (benzodiazepines or opiates) at Screening. Positive drug screen of BZDs, is allowed only if the use is intermittent and drug intake was 4 days or more before the visit (See Section 12.9.1)
14. Female patients must have had last natural menstruation ≥ 24 months before Screening OR be surgically sterile.
15. Male patients and their female spouse/partners who are of childbearing potential must agree to use highly effective methods of contraception, consisting of 2 forms of birth control (at least one of which must be a barrier method) starting at Screening, throughout the study and for 90 days post-last dose, OR be surgically sterile.
16. Patients who are taking medications for non-excluded concurrent medical conditions should be on a stable dose for at least 4 weeks before Screening. Patients taking allowed antidepressants (see Section 12.9) should be on a stable dose for at least 3 months before Screening and throughout the study
17. Patient has ability and commitment to spend at least 2 hours per day exposed to daylight (preferably outside but can be next to a window if weather or personal situation does not permit).
18. Participant and study partner have the ability to read and write in English or Spanish and have hearing, vision, and physical abilities adequate to perform assessments (corrective aids allowed).
19. Participant and study partner are fully vaccinated for COVID 19 including booster doses as indicated (6 months post second dose). Having been diagnosed with COVID 19 after completing the initial full Covid vaccine would meet the requirements for a booster shot

11.1.3 Exclusion Criteria

Potential patients who meet any of the following criteria will be excluded from participating in the study:

1. Declines whole genome screening for 2:107,510,000-107,540,000 polymorphism and APOE4 genotyping.
2. Patient is 2:107,510,000-107,540,000 polymorphism carrier.
3. Patient has an alternative cause for dementia other than AD.
4. A past or recent CT or MRI scan or report indicating any cortical infarct defined as > 1.5 cm^3; more than 2 lacunar-infarcts defined as ≤ 1.5 cm^3; or diffuse white matter disease (Fazekas score of more than 1 on MRI or CT Scan) (more details Appendix 3).
5. Patient has evidence of any clinically significant neurodegenerative disease, or other serious neurological disorders other than AD as detailed in Appendix 3,
6. Patient has a concurrent psychiatric disorder that prevents his/her participation in the trial including but not limited to a lifetime diagnosis of Schizophrenia, Bipolar

and related disorders, or Major Depressive Disorder, Substance and/or Alcohol use disorders within the past 2 years prior to Screening (See Appendix 3).

7. Patient has a history of uncontrolled or untreated cardiovascular, endocrine, gastrointestinal, respiratory, or rheumatologic disorders within the past 5 years.
8. Patients with a history of severe agitation within 12 months prior to Screening that requires (or has required) pharmacological treatment.
9. Patient has a history of serious infectious disease including:
   a. Neurosyphilis
   b. Meningitis
   c. Encephalitis
10. Patient has a history of a primary or recurrent malignant disease that has not been in remission for > 5 years prior to the Screening visit, with the exceptions of excised cutaneous squamous cell carcinoma in situ, basal cell carcinoma without recurrences; and history of intraductal breast cancer, cervical carcinoma in situ, or in situ prostate cancer resected over 5 years previously. (For resected in situ prostate cancer, i.e., high-grade intraepithelial neoplasia, the patient must have a normal prostate-specific antigen [PSA] prior to Screening and no increase in PSA since his resection surgery).
11. Patient has severe pain that is likely to interfere with sleep (in the opinion of the investigator).
12. Patient has any concomitant documented progressive disease likely to interfere with the conduct of the study, particularly:
    a. Liver disease with aspartate aminotransferase (AST), alanine aminotransferase (ALT) or gamma-glutamyltransferase (GGT) > 3 times the upper limits of normal (ULN)
    b. Total bilirubin > 3 times the ULN
    c. Mean corpuscular volume > 95 fl if due to chronic alcoholism
    d. Renal failure with creatinine < 30 ml / min / 1.73m^2
13. Patients that are taking prohibited medications according to Appendix 2 See also section 12.9.
14. Continuous use of benzodiazepines or other sedative-hypnotics during the 2 weeks before Screening (see Section 12.9).
15. Patient has a history of chronic use (more than 3 months of continuous use) and abuse of benzodiazepines or other sedative-hypnotics.
16. Use of any kind of melatonin/melatonin agonist during the 2 weeks before Screening (see Section 12.9).
17. Patient has known or suspected hypersensitivity to exogenous melatonin or melatonin receptor agonists.
18. Patient has clinically significant abnormal laboratory findings that have not been approved by the study safety officer.

19. Patient has persistent bradycardia (heart beat < 50 bpm) or tachycardia (heart beat > 100 bpm).
20. Patient has atrioventricular block (type II/Mobitz II and type III), congenital long QT syndrome, sinus node dysfunction or a marked prolongation of QTc interval (repeated demonstration in ECGs of QTc interval > 450 msec for males and > 470 msec for females using Fridericia's formula: QTc = QT/cube root of RR).
21. Patient has other serious diseases that could interfere with patient assessment, in the opinion of the investigator.
22. Patient has untreated B12 and/or folic acid deficiency.
23. Patient has participated in a clinical trial with any investigational agent within 3 months before Screening. Participants in any former monoclonal antibody clinical trial for AD are not eligible until 6 months after the last visit of the previous study. Patients who have received active vaccine for AD in the past will be excluded.
24. Patient with a body mass index (BMI) above 35 or below 18.
25. Lifestyle exclusions:

    a) Patients unwilling to limit alcohol intake to less than 30 g of pure alcohol per day (see Appendix 1) and to abstain after 2000h throughout the study

    a) Patients unwilling to be exposed to at least 2 hours of daylight each day
    b) Divergence from the accepted level of study medication compliance (70%-130% of expected consumption) as verified at Visit 2 (see Section 12.10)
    c) Patients consuming more than 7 cups of tea or coffee (or equivalent amount of caffeine [650 mg] in other caffeinated beverages) per day
    d) Patients with an irregular lifestyle or life pattern (e.g., shift workers, patients likely to be jet lagged)
26. Patients with evidence of serious risk of suicide based on the Columbia-Suicide Severity Rating Scale, i.e., active suicidal ideation with some intent to act, with or without a specific plan (a positive response to Suicidal Ideation Items 4 or 5) in the 6 months prior to Screening, **OR** with evidence of suicidal behavior in the 2 years prior to Screening (a positive response to any of the 5 Suicidal Behavior Items {actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior}), **OR** who, in the opinion of the investigator, present a serious risk of suicide.

11.1.4 Patient Eligibility Review

One of the keys to study success is validation of appropriate patient selection. Clinical review for patient eligibility and appropriate symptom severity level confirmation can enhance the subject selection process and optimize clinical trial outcomes. The mere presence of surveillance improves the integrity of subject selection given that sites are aware that a site-independent body is monitoring subject eligibility data.

The Clinical Surveillance & Training (CST) team is a division of Syneos Health. The CST Eligibility Review is an independent evaluation of the eligibility of the subject. Sites will work with CST to complete an Eligibility Review Packet at Screening. This review will include key medical and scales data (i.e. Laboratory Findings, ECG, Medical History, Physical Examination, Concomitant Medications, Psychiatric Intake Notes, CDR, MMSE, C-SSRS, as well as practice ADAS-Cog 14, CT/MRI reports and any other information necessary to establish patient eligibility per protocol).

CST will follow up with the site where necessary in order to ensure that eligibility is met. A decision to enroll a patient will be made by the investigator *only after* CST Eligibility Review is concluded. All communication regarding subject eligibility will be documented and filed.

While CST will exercise quality oversight to aid enrolment of the appropriate patients, the Investigator remains responsible for ensuring that subjects are eligible for enrollment into the trial.

11.1.5 Removal of Patients from Therapy or Assessments

Patients who fail to fulfill the enrollment criteria at the Visit 1 screening evaluation will be withdrawn from the study prior to receipt of any study medication.

Patients withdrawn from the study prior to randomization would be considered as “screen failure.”

Patients withdrawn from the study after randomization would be considered as “drop-out.”

Patients may withdraw their consent at any time during the study or may be withdrawn by the investigator at any time. Neurim Pharmaceuticals (1991) Ltd reserves the right to withdraw patients from the study on the grounds that a serious protocol violation has occurred. In case of dispute, the principal investigator’s opinion will prevail.

The date and reason for withdrawal as well as the data collected up to that time should be recorded in the electronic case report form (eCRF).

Patients who withdraw from the study after receiving any study medication will be required to return to the study site for a Premature Discontinuation Visit for safety assessments to be performed. Once a patient has been withdrawn, he/she may not re-enter the study, and the medication that was designated for this patient cannot be given to any other patient.

11.2 TIMINGS THROUGHOUT THE STUDY

11.2.1 Overall Study Schedule

It is intended to have an 18-month recruitment period. Each patient will undergo a 4-week, screening, no treatment plus 2-week, single-blind, run-in period and a 26-week, randomized, double-blind treatment period, for a total of 28 weeks. Participants who will complete the 26 weeks double blind study will be offered a 12 months extension during which all patients will be given 20 mg piromelatine nightly (double blind assignment will be kept). Two weeks after last dosing of study medication, the informant will receive a follow-up phone call. The duration of the study is expected to be approximately 40 months from first patient screened to final patient completing the study.

An integrated clinical study report in the format of the International Conference on Harmonization Tripartite Guideline E3: Structure and Content of Clinical Study Reports (ICH E3) will be written within 3 months of the last patient completing the study.

12. TREATMENTS

12.1 TREATMENTS ADMINISTERED

Throughout the study, all study medication is to be administered orally, 1 tablet daily, taken before going to bed, preferably between 2100h and 2300h, and after food consumption.

Upon completion of the 2-week, single-blind run-in period, patients will be randomly assigned to placebo and the active treatment arms (1:1) as follows:

Active Medication

Piromelatine 20 mg tablets

Placebo Medication

Matched placebo tablets, with identical features to the piromelatine tablets, will be used as control treatment

At the end of the study, each investigator will forward all unused medication packs together with any study medication that has not been allocated to the clinical supply vendor for destruction.

Piromelatine and matched placebo tablets are pink and oval shaped. Tablets will be packaged in polyethylene terephthalate bottles containing 35 tablets. Patients will receive sufficient medication at the Screening visit to provide enough tablets for the last 2 weeks run-in period before Visit 2. Patients will receive sufficient medication at the randomization visit (Visit 2) to provide enough tablets for the period of treatment between visits to allow for loss of tablets and for arrival at the scheduled visit up to 5 days after the scheduled date. For the period between Visit 2 (randomization) and Visit 3 (Week 13), each patient will receive 3 bottles with 35 tablets (total of 105 tablets). For the period between Visit 3 (Week 13) and Visit 4 (Week 26), each patient will receive 3 bottles containing 35 tablets each (total of 105 tablets). For the period between Visit 4 (Week 26) and Visit 5 (Week 39), each patient will receive 3 bottles containing 35 tablets each (total of 105 tablets). For the period between Visit 5 (Week 39) and Visit 6 (Week 52), each patient will receive 3 bottles containing 35 tablets each (total of 105 tablets). For the period between Visit 6 (Week 52) and Visit 7 (Week 78), each patient will receive 6 bottles containing 35 tablets each (total of 210 tablets).

12.2 IDENTITY OF INVESTIGATIONAL PRODUCTS

12.2.1 Piromelatine

Generic name:	piromelatine
Chemical name:	(N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-4-oxo-4H-pyran-2-carboxamide)
Formulation:	Microcrystalline cellulose Starch Colloidal silicon dioxide Magnesium stearate Opadry II 85F140041 Pink

The microcrystalline cellulose serves as a filler, starch is used as a binder, colloidal silicon dioxide is used as glidant, magnesium stearate serves as a lubricant, and pink Opadry II serves for film coating.

The study medication will be securely stored in the medical center's local pharmacy or in the investigator's office, separate from other drugs. It should not be exposed to sources of heat and is to be kept at room temperature (15°C-25°C, or 59°F-77°F). The study medication may not be used for any purpose other than the present study; the insurance coverage shall otherwise become null and void.

12.2.2 Placebo

The placebo is of identical appearance and formulation to the active piromelatine tablet but contains no active piromelatine.

12.2.3 Labelling Information

The study medication bottles will be labeled according to US Food and Drug Administration (FDA) requirements. The labeling on all bottles of study medication will include the following: name of sponsor, pharmaceutical dosage form, route of administration, quantity of dosage units, batch numbers, kit number, study number, patient ID number, directions for use, "for clinical trial use only", investigator name, storage method, the statement "keep out of reach of children," and "Caution: New Drug – Limited by Federal Law (US) to investigational use."

12.3 SELECTION OF DOSE IN THE STUDY

The choice of dose (20mg) to be orally administered in AD patients is defined according to the following clinical data.

In a Phase 1 study in healthy volunteers, piromelatine (2, 5, 20, 50, and 200 mg) was found to be safe and well tolerated with no SAEs and showed a favorable, dose-proportional PK profile following oral intake. In addition, piromelatine intake was associated with increase in total sleep time in the volunteers in a dose-dependent manner (Yalkinoglu, Zisapel et al. 2010). In a Phase 1b multiple ascending dose study in insomnia patients, piromelatine (2, 5, 20, and 50 mg) had a favorable PK profile without any sign of accumulation. This study also showed that piromelatine had some beneficial effects on sleep continuity measures and did not have an adverse effect on memory (Laudon, Katz et al. 2012). In a Phase 2, randomized, placebo-controlled, sleep laboratory study in insomnia patients (aged 18-80 years), piromelatine (20 and 50 mg daily for 1 month) enhanced sleep maintenance (WASO) measured by PSG significantly in comparison to placebo (Neurim press release, 2013). The 20 mg was a fully effective dose in the elderly (age 55 years and older). Piromelatine enhanced NREM Δ power (deep sleep) and decreased NREM β power, a fast EEG activity that is considered to be related to the hyperarousal state experienced by insomniac patients (Merica, Blois et al. 1998). Both effects may be beneficial for AD patients to enhance Aβ clearance from the brain. In a Phase 2, randomized, placebo-controlled, dose-ranging study of piromelatine (5, 20, and 50 mg daily for 6 months) in patients with mild dementia due to Alzheimer's disease (n=352 age 60-85 years) there were no statistically significant differences between the placebo and piromelatine groups in the changes from baseline in the primary not secondary endpoints in the full analysis set. No safety concerns were observed in this study and no specific trends in AEs by treatment group or piromelatine dose were noted.

However, GWAS identified an association between enhancement with piromelatine in cognitive functioning as assessed by cNTB and the presence of 5 to 6 single nucleotide polymorphisms in chromosome 2, 2:107,510,000-107,540,000 locus (2:107,510,000-107,540,000 polymorphism) comprising 27% of the study cohort. In a subsequent post hoc analysis, it was found that the participants with 2:107,510,000-107,540,000 polymorphism had significant worsening on ADAS-Cog14 and PSQI with piromelatine 20 mg compared to placebo. This worsening calls for exclusion of 2:107,510,000-107,540,000 polymorphism carriers from future studies of piromelatine in mild dementia due to Alzheimer's Disease.

In contrast, Piromelatine was efficacious vs placebo in 2:107,510,000-107,540,000 polymorphism non-carriers; the 20 mg dose was sufficient to evoke the full response.

12.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Commencing at Visit 1, all patients will be assigned an identification number which is comprised of a total 6 digits (first three numbers are site number, and last three numbers are subject number). This identification number must appear on all patient-related documents submitted to Neurim Pharmaceuticals. When qualified for enrollment at Visit 2, the patient will be randomly assigned to 1 of 2 trial arms.

12.5 SELECTION AND TIMING OF DOSE FOR EACH PATIENT

Upon completion of eligibility review, the informant will be instructed via telephone call to begin administration of study medication the period between screening visit and placebo run-in would be 4-weeks. The patient will take the first dose of placebo that evening. After 2 weeks of single-blind placebo run-in, the patient will be randomly assigned to receive either piromelatine (20 mg) or placebo. The patient will take the first dose of piromelatine/placebo in the evening of Visit 2. The dose of medication will be 1 tablet daily in the evening after meals, before going to bed, preferably between 2100h and 2300h. In the extension period, all patients will receive piromelatine (20 mg) regardless of the randomization group.

12.6 DOSE ADJUSTMENT CRITERIA

The dose will not change throughout the treatment period.

12.7 BLINDING

The initial 4-week screening period of this study are without any treatment. The second 2-week run-in period is designed as single blind, with the patient blinded to the medication he/she is receiving. All patients will receive placebo during the run-in period. The run-in will be followed by 26 weeks of double-blind treatment, and a 52 weeks extension period where the investigators, staff, and patients will be unaware of the initial allocated treatment.

The blinding will not be broken (unless in an emergency) until all completed eCRFs have been received by data management and the database is locked.

In case of an emergency, the investigator may access patient treatment assignment through the interactive web response system (IWRS). This will be done only when the investigator decides that knowledge of the treatment arm is required. Except in emergency cases, treatment assignment should not be accessed without discussion with the sponsor's safety officer. The date and reasons

for accessing treatment assignment must be fully documented, and a statement that the correct procedure was followed should be documented in the trial master file.

12.8 GENETIC TESTING FOR APOE4 STATUS AND SNPS POLYMORPHISM

C2N Diagnostics will use its LC-MS/MS platform to quantify various plasma-based biomarkers along with ApoE proteotype according to the unique sample ID#s.

1. Rapid TAT-Screening Plasma ApoE proteotype: C2N will identify ApoE proteotype that will be used for stratification of the placebo and active arms

2. Batched-Longitudinal Plasma Aβ42, Aβ40, and APS calculation: C2N will quantify plasma Aβ42, Aβ40 concentrations, calculate Aβ42/40, and the Amyloid Probability Score (APS).

3. Plasma pTau Multiple Analyte Assay (MAA): C2N will quantify pTau181, pTau217, total Tau (all pg/mL), and percent phosphorylation at Tau181 and Tau217 at screening and at Visit 7.

Screening for 2:107,510,000-107,540,000 polymorphism is needed for as an exclusion criterion. Retrospective genetic information could be used.

12.9 PRIOR AND CONCOMITANT THERAPY

Patients receiving acetylcholinesterase inhibitors for the treatment of AD must have been taking the medication for at least 6 months before Baseline (Visit 2), the daily dose must have remained unchanged for 4 months prior to Baseline, and the dose must not be expected to change during study participation.

Patients who stopped receiving acetylcholinesterase inhibitors before enrollment must be stable off acetylcholinesterase inhibitors for 3 months before Baseline and must be agreeable to not restarting throughout the study.

Patients not receiving acetylcholinesterase inhibitors must be agreeable to not starting it throughout the study.

Patients taking memantine (with or without acetylcholinesterase inhibitors) must be on a stable dose for at least 4 months before Baseline and plan to continue throughout the study.

Patients taking antidepressants should be on a stable dose for at least 3 months before the Screening visit (Visit 1) and throughout the study.

The following medications are not allowed during the study or during the 5 weeks before the Screening visit (Visit 1):

- **Fluvoxamine**
- **Mirtazapine**
- **Trazodone**
- **Insulin**
- **ADUHELM**

A full list of prohibited medication is listed in Section 24, APPENDIX 2 "PROHIBITED AND RESTRICTED MEDICATIONS."

Patients taking alternative pharmacotherapy for dementia (e.g., Souvenaid, DHA [docosahexaenoic acid], phosphatidylserine, omega-3 fatty acids, ginkgo biloba, ginseng, Huperzia serrata, vitamin B, vitamin D, vitamin E, or any other supplement to improve cognitive function) should be on a stable dose for at least 3 months before the Screening visit (Visit 1).

Other necessary and permitted concomitant treatment should not be altered if it has been established and equilibrated for at least 4 weeks prior to study enrollment, unless the investigator(s) consider(s) that a change is necessary. This should first be discussed with the sponsor's safety officer who will assess whether the patient is to be withdrawn.

Continuous use of sedative-hypnotics or treatments used as a hypnotic (e.g., all benzodiazepines, zopiclone, zolpidem and zaleplon, barbiturates, buspirone and hydroxyzine, melatonin or melatonin agonists [ramelteon]) is not allowed during the study or during the 2 weeks before the Screening visit (Visit 1).

12.9.1 Rescue Medication

Intermittent use of short to medium-acting benzodiazepines, melatonin (up to 3 mg), ramelteon (up to 8 mg), eszopiclone (up to 2 mg), zaleplon (up to 5 mg) or zolpidem tartrate (≤ 6.25 mg controlled release and ≤ 10 mg tablet) is allowed when absolutely necessary for intermittent sleep disturbances. Intermittent use is defined as no more than 2 times a week. However, these medications cannot be used within 3 days of any study visit. Depending on which short or intermediate acting Benzodiazepine is used it is possible that a positive Urine Drug Screen could result even if the patient took it 4 days or more before the visit. In cases that a patient uses benzodiazepines intermittently according to the definition under this section (12.9.1) and took the last dose 4 days or more before any visit and urine drug screen is still positive – this patient would be eligible for the study.

12.10 TREATMENT COMPLIANCE

Treatment compliance will be calculated at each study visit by the investigator counting returned tablets and using the formula:

$$\text{Compliance (\%)} = \frac{\text{number of tablets actually taken}}{\text{number of days since last visit}} \times 100$$

Compliance between Visit 1 and Visit 2 should be calculated using number of days since start of run-in.

Any divergence from the accepted level of compliance (70%-130% of expected consumption) is to be investigated by the investigator and should lead to withdrawal of the patient from the study.

Treatment compliance will be recorded in the eCRF by the investigator.

13. ASSESSMENTS

The table in Section 10.1 presents the assessments that are planned to be conducted throughout the study.

Prescreening (telephone call)

Investigators should clarify to potential patients the requirements of concomitant medications as specified in Section 12.9.

Visit 1 - Screening (Day —42 ± 5)

- Explanation of the study
- Patient and informant will both be given an ICF to read and sign. Legally authorized representatives will not be allowed in this protocol unless the ICF has been signed by them in addition to the patient as dictated by legal circumstances.
- Allocation of screening number
- Eligibility screening:
    1. MMSE completed by the investigator or investigator designee with the patient
    2. CDR completed by the investigator or investigator designee with the patient and informant
    3. Recording of demographic data (date of birth, sex, tobacco and alcohol use, substance abuse)
    4. Detailed medical and surgical history
    5. Physical examination and vital signs measurements, including weight and 12-lead ECG
    6. Examination of CT/MRI scans
    7. Examination of positron emission tomography (PET)/CSF data (for patients who have this information)
    8. Inclusion and exclusion criteria
- Collection of blood and urine samples for urinalysis, hematology, biochemistry, and hormonal tests
- Collection of blood sample for 2:107,510,000-107,540,000 polymorphism
- Collection of blood sample for PrecivityAD™ test including rapid TAT-Screening Plasma ApoE proteotype, batched-Longitudinal Plasma Aβ42, Aβ40, and APS calculation and pPlasma pTau Multiple Analyte Assay (MAA)
- Urine drug screen for benzodiazepines and opiates
- Recording of concomitant medication(s)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Practice session with ADAS-cog14

- Uploading MMSE, CDR, ADAS-cog, and documented history of cognitive deterioration for central review by the Clinical Surveillance & Training team.
- Dispensing of study medication (placebo) – informant will be instructed via telephone call to open the bottle and start the run-in period upon confirmation of eligibility. The drug can also be kept at site and be dispensed at any point in the screening period or once eligibility is confirmed. The patient will be asked to bring all medication packs, including empty packs, with him/her to Visit 2.

Visit 1 may be completed over 2 consecutive days (no Friday/Monday visits) at the discretion of the investigator. Both the patient and informant must be present both days, and the following screening procedures should be completed on the indicated day:

- Screening Day 1: MMSE, ADAS-cog,
- Screening Day 2: CDR, C-SSRS

Post Visit 1 (–14) - This time point becomes Day –14 regardless of the time it took to reach it

Upon completion of eligibility review, the informant will be instructed via telephone call to open the bottle and start the run-in period. Should eligibility review and/or laboratory results show that a patient can no longer be considered eligible, the unopened run-in bottle will be collected from the patient. Ineligible patients who accidently open run-in bottles and consume run-in placebo tablets will be invited to a premature discontinuation visit (see below).

Visit 2 - Baseline (Day 0 ± 5 days [from the end of run-in])

- Review of 2:107,510,000-107,540,000 polymorphism and
- Review of PrecivityAD™ test results
- Vital signs measurements
- Verification of relevant inclusion/exclusion criteria (see Section 11.1.2 and Section 11.1.3)
- Recording of concomitant medication(s)
- Recording of adverse events (AEs) (see Section 14.1)
- Review of Visit 1 clinical laboratory results
- Compliance verification
- Allocation of randomization number
- Collection of all unused study medication and used bottles since last visit
- ADCS-CGIC completed by an investigator designee (should not be completed by the principal investigator) with the patient and informant; the ADCS-CGIC assessor must be blinded to all other data for the patient after Visit 2
- ADCS-ADL completed by the investigator or investigator designee with the informant
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- MMSE completed by the investigator or investigator designee with the patient

- NPI completed by the investigator or investigator designee with the informant
- PSQI completed by the investigator or investigator designee with the patient and informant
- CDR-SB completed by the investigator or investigator designee with the patient and informant
- Dispensing of study medication
- The patient will be asked to bring all medication packs, including empty packs, with him/her to Visit 3.

Pre-Visit 3

On Days 7 ± 3, 14 ± 3, 21 ±3, 28±3, 35 ± 3, 42 ± 3, 49 ± 3, 56 ± 3, 63 ± 3, 70 ± 3, 77 ± 3, and 84 ± 3, the informant will be called by study personnel for follow-up and for safety and compliance verification purposes (eg, study medication compliance, daylight exposure compliance, and AE/concomitant medication checks).

Visit 3 - Week 13 (Day 91 ± 5 days)

- Physical examination and vital signs measurements,
- Recording of concomitant medication(s)
- Recording of AEs (see Section 14.1)
- Collection of blood and urine samples for urinalysis, hematology and biochemistry tests
- Urine drug screen for benzodiazepines and opiates (to be repeated randomly in some patients during the study)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Compliance verification
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- ADCS-CGIC completed by an investigator designee (should not be completed by the principal investigator) with the patient and informant; the ADCS-CGIC assessor must be blinded to all other data for the patient after Visit 2
- ADCS-ADL completed by the investigator or investigator designee with the informant
- PSQI completed by the investigator or investigator designee with the patient and informant
- Collection of all unused study medication and used bottles since last visit
- Dispensing of study medication
- The patient will be asked to bring all medication packs, including empty packs, with him/her to Visit 4

Pre-Visit 4

On Days 98 ± 3, 105 ± 3, 112 ± 3, 119 ± 3, 126 ± 3, 133 ± 3, 140 ± 3, 147 ± 3, 154 ± 3, 161 ± 3, 168 ± 3, and 175 ± 3 the informant will be called by study personnel for follow-up and for safety

and compliance verification purposes (eg, study medication compliance, daylight exposure compliance, and AE/concomitant medication checks).

Visit 4 – Week 26 (Day 182 ± 5 days)

- Physical examination and vital signs measurements, including 12-lead ECG
- Recording of concomitant medication(s)
- Recording of AEs (see Section 14.1)
- Collection of blood and urine samples for urinalysis, hematology, biochemistry (including B12), and hormonal tests
- Body weight measurement
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Compliance verification
- MMSE completed by the investigator or investigator designee with the patient
- ADCS-CGIC completed by investigator designee (should not be completed by the principal investigator) with the patient and informant; the ADCS-CGIC assessor must be blinded to all other data for the patient after Visit 2
- ADCS-ADL completed by the investigator or investigator designee with the informant
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- NPI completed by the investigator or investigator designee with the informant
- PSQI completed by the investigator or investigator designee with the patient and informant
- CDR-SB completed by the investigator or investigator designee with the patient and informant
- Collection of all unused study medication and used bottles since last visit
- Dispensing of study medication
- The patient will be asked to bring all medication packs, including empty packs, with him/her to Visit 5

Pre-Visit 5

On Days 196 ± 5, 210±5, 224 ± 5, 238 ± 5 and 252 ± 5 the informant will be called by study personnel for follow-up and for safety and compliance verification purposes (eg, study medication compliance, daylight exposure compliance, and AE/concomitant medication checks).

Visit 5 - Week 39 (Day 273 ± 5 days)

- Physical examination and vital signs measurements,
- Recording of concomitant medication(s)

- Recording of AEs (see Section 14.1)
- Urine drug screen for benzodiazepines and opiates (to be repeated randomly in some patients during the study)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Compliance verification
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- ADCS-ADL completed by the investigator or investigator designee with the informant
- PSQI completed by the investigator or investigator designee with the patient and informant
- Collection of all unused study medication and used bottles since last visit
- Dispensing of study medication
- The patient will be asked to bring all medication packs, including empty packs, with him/her to Visit 6

Pre-Visit 6

On Days 287 ± 5, 301 ± 5, 315 ± 5, 329 ± 5, 343 ± 5 and 357 ± 5, the informant will be called by study personnel for follow-up and for safety and compliance verification purposes (eg, study medication compliance, daylight exposure compliance, and AE/concomitant medication checks).

Visit 6 - Week 52 (Day 364 ± 5 days)

- Physical examination and vital signs measurements,
- Recording of concomitant medication(s)
- Recording of AEs (see Section 14.1)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Compliance verification
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- ADCS-ADL completed by the investigator or investigator designee with the informant
- PSQI completed by the investigator or investigator designee with the patient and informant
- Collection of all unused study medication and used bottles since last visit
- Dispensing of study medication
- The patient will be asked to bring all medication packs, including empty packs, with him/her to Visit 5

Pre-Visit 7

On Days 378 ± 5, 392 ± 5, 406 ± 5, 420 ± 5, 434 ± 5, 448 ± 5, 462 ± 5, 476 ± 5 and 490 ± 5, the informant will be called by study personnel for follow-up and for safety and compliance

verification purposes (eg, study medication compliance, daylight exposure compliance, and AE/concomitant medication checks).

Visit 7 – Week 78 (Day 546 ± 5 days)

- Physical examination and vital signs measurements, including 12-lead ECG
- Recording of concomitant medication(s)
- Recording of AEs (see Section 14.1)
- Collection of blood and urine samples for urinalysis, hematology, biochemistry, and hormonal tests
- Collection of blood sample for plasma pTau Multiple Analyte Assay (MAA)
- Body weight measurement
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Compliance verification
- MMSE completed by the investigator or investigator designee with the patient
- ADCS-CGIC completed by investigator designee (should not be completed by the principal investigator) with the patient and informant; the ADCS-CGIC assessor must be blinded to all other data for the patient after Visit 2
- ADCS-ADL completed by the investigator or investigator designee with the informant
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- NPI completed by the investigator or investigator designee with the informant
- PSQI completed by the investigator or investigator designee with the patient and informant
- CDR-SB completed by the investigator or investigator designee with the patient and informant
- Collection of all unused study medication and used bottles since last visit

Order of scale administration

For each study visit, it is recommended that the scales be conducted in the following order.

Patient:

Visit 1: MMSE, CDR, C-SSRS, ADAS-Cog

Visit 2: MMSE, ADAS-Cog, CDR, ADCS-CGIC, PSQI

Visit 3: ADAS-Cog, ADCS-CGIC, C-SSRS, PSQI

Visit 4: MMSE, ADAS-Cog, CDR, ADCS-CGIC, C-SSRS, PSQI

Visit 5 and 6: ADAS-Cog, C-SSRS, PSQI

Visit 7: MMSE, ADAS-Cog, CDR, ADCS-CGIC, C-SSRS, PSQI

Informant:

Visit 1: CDR

Visit 2: CDR, ADCS-CGIC, ADCS-ADL, PSQI (with patient), NPI

Visit 3: ADCS-CGIC, ADCS-ADL, PSQI (with patient)

Visit 4: CDR, ADCS- CGIC, ADCS-ADL, PSQI (with patient) NPI

Visit 5-6: ADCS-ADL, PSQI (with patient)

Visit 7: CDR, ADCS-CGIC, ADCS-ADL, PSQI (with patient) NPI

IMPORTANT NOTE:

***Only raters with a "Qualified" status (in the Site Status Memo that each site receive occasionally from Syneos Health) are permitted to rate the associated scales including the Clinical History form in the study.**

Safety Follow-up

Two weeks after the last dose of study medication, a telephone call will be made to the informant to elicit any safety concerns for the purpose of recording AEs.

Premature Discontinuation Visit

The investigator will record premature discontinuation reason and will order the patient a laboratory test request (hematology, biochemistry and urinalysis), the results of which should be recorded by the investigator when they become available. This visit also includes:

- Collection of all unused study medication and used bottles since last visit
- Physical examination and vital signs measurements, including 12-lead ECG
- Collection of blood and urine samples for urinalysis, hematology, biochemistry, and hormonal tests
- Recording of concomitant medication(s)
- Recording of AEs
- ADCS-i-ADL completed by the investigator or investigator designee with the informant
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- C-SSRS

Premature Discontinuation Visit prior to Randomization

Ineligible patients who accidently open run-in bottles and consume run-in placebo tablets will be invited to a premature discontinuation visit, which will include:

- Collection of accidentally used run-in bottle
- Physical examination and vital signs measurements
- Recording of AEs

Unscheduled visits

Unscheduled visits are additional visits to the planned visits in the study. They do not replace the regular, scheduled visits. An unscheduled visit can be arranged at any time during the study triggered by the investigator or the subject for safety reasons (e.g. adverse event/adverse event follow-up) that need an onsite examination (physical examination, laboratory evaluation, concomitant medications review etc.).

13.1 CLINICAL EFFICACY PARAMETERS

13.1.1 Primary Efficacy Parameter

The primary efficacy parameter is the

ADAS-cog14

The ADAS was designed to measure the severity of the most important symptoms of AD. Its subscale, ADAS-cog, is the most popular cognitive testing instrument used in clinical trials. It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention, and other cognitive abilities that are often referred to as the core symptoms of AD. The test comprises 11 items summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment. A negative change indicates an improvement from baseline. The addition of delayed recall, number cancelation, and maze tasks – and thus turning ADAS-cog into a 12-, 13-, and 14-item scale respectively – has increased the ability to detect changes in patients in the early stages of the disease (Sano, Raman et al. 2011).

13.1.2 Secondary Efficacy Parameters

ADCS-ADL

The entire ADCS-ADL scale will be administered, however only the instrumental activities of daily living items (items 7 to 23) will be analyzed. The ADCS-iADL is one out of several available measurements of the Activities of Daily Living (ADL) in the targeted study population (Gold 2012), and it is based on the work of the ADCS operating in the US (Galasko, Bennet et al. 2006). The iADLs are thought to be more affected as the disease progresses. The range for the iADL score is 0 to 56, with lower scores indicating greater disease severity. Scale administration duration will be about 15-30 minutes.

ADCS-CGIC

The ADCS-CGIC is a systematic method for assessing clinically significant change in a clinical trial as viewed by an independent skilled and experienced clinician. The ADCS-CGIC focuses on clinicians' observations of change in the patient's cognitive, functional, and behavioral performance since the beginning of a trial. It relies on both direct examination of the patient and interview of informants. Unlike a targeted symptom scale, it takes into account a patient's overall function in the cognitive, behavioral, and functional activity domains. Scoring is based on an interview with the informant and examination of the patient by an independent evaluator, without

consulting other information such as cognitive test results. The ADCS-CGIC requires the assessor to consider a number of cognitive, functional, and behavioral areas prior to providing an overall "global" assessment of clinical change (Schneider, Olin et al. 1997, Schneider, Clark et al. 2006). The ADCS-CGIC assessor must be blinded to all other data for the patient after Visit 2.

MMSE

The MMSE is a brief assessment instrument used to assess cognitive function in elderly patients. The MMSE can be used to screen for cognitive impairment and as a measurement of cognition over time and with pharmacologic treatment. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention: the maximum score is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures: the maximum score is 9. The scoring range for the MMSE is 0-30. The MMSE was shown to be both reliable and valid in a group of elderly subjects, including those with dementia, depression with cognitive impairment, depression, and “normal” elderly patients. The MMSE has been shown to possess sensitivity and specificity in various populations. Although the MMSE alone is unable to provide diagnostic information, the data on its sensitivity and specificity in cognitively impaired patients demonstrates its utility as a screening instrument.

iADRS

The integrated Alzheimer’s Disease Rating Scale (iADRS) combines scores from the 2 widely accepted measures, the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and the Alzheimer’s Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL). (iADRS), (Wessels et al., 2015) The iADRS has been shown to perform better than most composites and scales in detecting disease progression and comparably or better than individual scales in detecting treatment differences. The iADRS can be divided into two principal components primarily representing cognitive items and instrumental ADLs. Dynamic ranges of the subscales were similar across all studies, reflecting approximately equal contributions from both subscales to the iADRS total score. In item analyses, every item contributed to the total score, with varying strength of contributions by item and across data sets. The iADRS demonstrated acceptable psychometric properties and was effective in capturing disease progression from MCI through moderate AD and treatment effects across the early disease spectrum. These findings suggest the iADRS can be used in studies of mixed populations, ensuring sensitivity to treatment effects as subjects progress during studies of putative disease-modifying agents. In the present study iADRS score will be calculated from the ADAS-cog14 and ADCS-iADL scores using the equation (Wessels, Siemers et al. 2015)

iADRS score=[-1*(ADAS-cog14score)+90]+iADLscore

NPI

The scale consists of 12 domains that are rated for both frequency (range 1-4) and severity (range 1-3). A composite score for each domain is calculated (frequency × severity), which ranges from 1 to 12. There is a leading question for each item. If the symptom is not present then the frequency, severity, and distress scores are not completed. In this case, the score is 0 for the item. The sum of the composite scores yields the NPI-12 total score (range 0-144). A negative change in score indicates an improvement from baseline (symptom reduction) (Cummings, Mega et al. 1994).

PSQI

The PSQI is an effective instrument used to measure the quality and patterns of sleep in the older adult. It differentiates "poor" from "good" sleep by measuring 7 areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The investigator with the patient and informant rate each of these 7 areas of sleep. In cases of discrepancies, the informant answers prevail. Scoring of answers is based on a 0 to 3 scale, whereby a score of 3 reflects the negative extreme on the Likert Scale. A global sum of 5 or greater indicates a "poor" sleeper (Buysse, Reynolds et al. 1989).

13.1.3 Exploratory Efficacy Parameters

CDR-SB

The Clinical Dementia Rating (CDR) is a well validated instrument that has been in use for more than 20 years in clinical trials in AD and MCI. The CDR assesses three domains of cognition (memory, orientation, judgment/ problem solving) and three domains of function (community affairs, home/hobbies, personal care) using structured interviews of both the study subject and a companion/informant carried out by a trained rater and scored using a standard methodology. The scores for the six domains (range from 0 to 3) tested can be summed (CDR Sum of Boxes or CDR-SB);

ADAS-cog13, ADAS-cog12, and ADAS-cog11

The ADAS was designed to measure the severity of the most important symptoms of AD. Its subscale, ADAS-cog, is the most popular cognitive testing instrument used in clinical trials. It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention, and other cognitive abilities that are often referred to as the core symptoms of AD. The test comprises 11 items summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment. A negative change indicates an improvement from baseline. The addition of delayed recall, number cancelation, and maze tasks – and thus turning ADAS-cog into a 12-, 13-, and 14-item scale respectively – has increased the ability to detect changes in patients in the early stages of the disease (Sano, Raman et al. 2011).

Columbia-Suicide Severity Rating Scale (C-SSRS) The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment developed by multiple institutions, including Columbia University, with NIMH support. The scale is evidence-supported and is part of a national and international public health initiative involving the assessment of suicidality.

13.2 APPROPRIATENESS AND CONSISTENCY OF MEASUREMENTS

These efficacy measurements have been used in other studies in elderly patients and AD patients.

13.3 CLINICAL SAFETY PARAMETERS

The safety parameters assessed at each visit will include spontaneously reported AEs or SAEs, vital signs measurements (temperature, heart rate and blood pressure), physical examination, body

weight, and clinical laboratory tests (hematology, biochemistry, and urinalysis). A 12-lead ECG will be performed at Visit 1 (Screening), Visit 4 (Week 26), and Visit 7 (Week 78; end-of-study visit).

C-SSRS

Suicidal ideation will be rated at Visit 1 (Screening), at Visits 3-7 (Weeks 13-78), and at premature discontinuation visit using the C-SSRS. At Screening patients with evidence of serious risk of suicide based on the Columbia-Suicide Severity Rating Scale (C-SSRS), i.e., active suicidal ideation with some intent to act, with or without a specific plan (a positive response to Suicidal Ideation Items 4 or 5) in the 6 months prior to Screening, OR with evidence of suicidal behavior in the 2 years prior to Screening (a positive response to any of the 5 Suicidal Behavior Items {actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior}), OR who, in the opinion of the investigator, present a serious risk of suicide, will be recorded as screen failures. Subsequent change from Screening on the C-SSRS will be summarized by study visit.

13.3.1 Routine Laboratory Procedures

All blood and urine samples will be analyzed using a central laboratory. An operating manual specifying all the steps for the urine and blood sampling will be given to the person in charge of the sampling.

The sampling will be performed at the site at Visits 1 (Screening), 3, and 4, 7 and as soon as possible following the Premature Discontinuation Visit (if applicable).

The following parameters will be measured for hematology: hemoglobin, hematocrit, red blood cells, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cells, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets.

The following parameters will be measured for biochemistry: creatinine, uric acid, urea, AST, ALT, albumin, GGT, total protein, sodium, potassium, chloride, calcium, phosphorus, glucose, alkaline phosphatase, and total bilirubin. B12 will be measured at Visit 4.

Prolactin and testosterone levels will be measured from blood samples collected at Visits 1, 4, 7 and premature discontinuation visit.

14. SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

14.1 ADVERSE EVENTS

The recording of AEs is an important aspect of study documentation. Detailed guidelines are set out below.

14.1.1 Eliciting and Documenting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study.

14.1.2 Definitions of Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a study drug and which does not necessarily have a causal relationship with the study drug and whether or not considered drug related.

An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes, whether associated with the study medication and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments.

Following are not reported as adverse event:
• Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, which do not represent a clinically significant exacerbation or worsening
• Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
• Pre-existing disease or medical condition that does not worsen.
• Situations in which an adverse change has not occurred, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
• Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose must be mentioned in the Study Drug Log.

Patient entry into the study is defined as the time at which informed consent is obtained (this must be before any protocol-specific diagnostic procedures or interventions are performed).

Adverse events will be elicited by asking the patient a nonleading question, for example “Have you experienced or are you experiencing any new or changed symptoms since we last asked/since your last visit?”

14.1.3 Reporting of Adverse Events

All AEs subsequent to Visit 1 must be reported <u>regardless of whether or not they are considered drug related</u>.

Adverse events should be reported on the appropriate AE page of the eCRF.

14.1.4 Assessment of Severity

Each AE will be assigned a category as follows:

Mild: The AE was not sufficiently intense to result in discontinuation of the drug. Symptomatic treatment may have been given.

Moderate: The AE was sufficiently intense to result in discontinuation of the drug. Symptomatic treatment may have been given.

Severe: Severe is more intense than moderate; moreover, the AE interferes significantly with ability to do work or usual activity.

A mild, moderate or severe AE may or may not be serious. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations

If there is a change in severity of an AE, it must be recorded as a separate event.

14.1.5 Assessment of Frequency

Frequency should be assessed using the following categories:

- unique
- intermittent
- continued

14.1.6 Assessment of Outcome

Outcome should be assessed using the following categories:

- recovered
- recovered with sequelae
- not recovered
- unknown

14.1.7 Assessment of Causality

Every effort should be made by the investigator to explain each AE and assess its relationship, if any, to study medication treatment. Causality should be assessed using the following categories:

Related to study drug: AE that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out).

Including:

• The event occurred in close temporal relationship to study drug administration.

• The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.

• The event re-occurred when treatment was re-introduced.

• Environmental factors such as clinical state and other treatments could equally have caused the event.

Related AEs should be considered as one of the following categories:

Definite	The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
Probable	Reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically

	reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
Possible	Reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unrelated to study drug: This category applies to any AE (serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

Unrelated AEs should be considered as one of the following categories:

Unlikely	Temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations
Unrelated	Clearly not related to drug administration.

14.1.8 Follow-up of Adverse Events

All investigators should follow-up with patients on AEs and SAEs until the event/pregnancy is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it.

14.2 SERIOUS ADVERSE EVENTS

14.2.1 DEFINITION OF A SERIOUS ADVERSE EVENT

An SAE is any event that is:

1. Fatal
2. Life threatening

   An AE is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form.

3. Disabling or incapacitating

   An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

4. Results in hospitalization or prolongs a hospital stay

   Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing, nonworsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history/physical examination page of the eCRF.

5. Is a congenital anomaly or birth defect

6. In addition, medical and scientific judgment is required to decide if prompt notification is required in other situations; i.e., any event which the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above, or which would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the drug.

14.2.2 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

An unexpected AE is defined as any AE that is not expected, i.e., one that has not been reported as expected in this protocol or in the investigator's brochure, either from previous clinical or preclinical studies.

14.2.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the last dose of study medication, whether or not the SAE is related to the study medication/placebo.

SAEs occurring during study drug administration, i.e., between study drug initiation and EOS after study drug discontinuation, are defined as treatment emergent SAEs.

An SAE report is reported by completing the SAE or Pregnancy Report Form

The completed SAE or Pregnancy Report Form must be emailed or faxed to the Safety team within 24 hours of becoming aware of an SAE or follow-up information that pertains to an SAE.

Syneos Health will inform Neurim Pharmaceuticals – both Clinical team and Pharmacovigilance team (section 14.2.5) of any deaths, life-threatening SAEs, or drug-related SAEs within 1 working day and within 2 working days for all other SAEs. The investigator should not wait to receive additional information to fully document the event before notifying of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time

after cessation of study medication and linked by the investigator to this study, should be reported to the study monitor and Safety team immediately.

SAEs are reported on SAE forms and also on AE pages in the eCRF. Therefore, they are entered both in the drug safety and clinical databases and must be reconciled before study closure.

14.2.4 REPORTING OF SUSARS

Suspected (considered related to the study drug) and Unexpected (not previously described in the reference safety document), Serious Adverse Reactions (SUSARs) will be expedited by Syneos Health to Health Authorities, ECs/IRBs and investigators, as appropriate. SUSARs will not be subject to systematic unblinding.

The reference safety document to assess whether or not an SAE should be reported to Health Authorities, ECs/IRBs and investigators in an expedited fashion is the Investigator's Brochure.

Neurim Pharmaceuticals – both Clinical team and Pharmacovigilance team will be informed regarding SUSARs before the expedition to the Health Authorities, ECs/IRBs and investigators

14.2.5 MEDICAL ASSISTANCE

If there is a need to discuss any medical issues concerning an SAE, then the medical monitor for the study can be contacted at:

Name: David C Subich, MD
Title: Medical Director
Company: Syneos Health
Email: david.subich@syneoshealth.com
Office: 984-459-5075
Mobile: 706-905-0866
Fax: 239-344-8586

In addition, the sponsor's clinical VP and safety officer can be contacted at:

Name: Tali Nir, DVM
Title: VP, Clinical and Regulatory Affairs
Company: Neurim Pharmaceuticals (1991) Ltd
Mail: talin@neurim.com
Tel: 972-3-7684902
Fax: 972-3-6494568

Name: Ksenia Shapiro
Title: Head of Global Quality & Pharmacovigilance
Company: Neurim Pharmaceuticals (1991) Ltd
Mail: ksenias@neurim.com
Tel: 972-3-7694139
Fax: 972-3-6494568

14.2.6 REGULATORY RESPONSIBILITY

Syneos Health, on behalf of Neurim Pharmaceuticals, has a responsibility to notify the regulatory authorities about the safety of a new drug and will also inform all participating investigators of serious and/or unexpected drug-related events associated with the use of this drug. Therefore, prompt notification of SAEs is required by the investigator so that reporting timelines can be met, and to ensure ethical responsibilities towards the safety of other patients are met. The investigators must adhere to local requirements of the IRBs and independent ethics committees with regard to reporting these events locally.

15. STUDY TERMINATION CRITERIA

Neurim Pharmaceuticals reserves the right to discontinue the study at any time. The reasons will be discussed with the investigators. A study site may also be discontinued by Neurim Pharmaceuticals for significant deviations from the protocol or due to insurmountable difficulties experienced in running the study at that center.

16. DATA COLLECTION AND ENTRY

The study will be monitored at regular intervals during the enrollment and follow-up period. There will be a monitoring visit or telephone call approximately every 8 weeks. The frequency of monitoring visits will be determined by the rate of patient recruitment.

The following will be reviewed at these visits:

- Compliance with the protocol
- Consent procedure
- Source document verification (see below)
- AE procedures
- Storage and accountability of materials

A 21CFR11 compliant e-CRF/EDC system will be used for data capture. Data should be entered into the system timely after the patient has attended a visit or after the data become available, as applicable. It is the responsibility of the investigator to maintain adequate and accurate eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. All eCRFs should be completed in their entirety.

The purpose of source document verification is to verify, so far as is possible, that the information in the eCRF reflects the data recorded in the patient's medical notes (see Section 21.2 for details). Source document verification will be performed with due regard for patient confidentiality and will be undertaken on an ongoing basis as part of the monitoring visits. Direct access to the source documents will be required. The monitor will make a direct comparison with data entered in the eCRFs.

The investigator must permit the monitor, the sponsor's internal auditors, and representatives from the regulatory authorities, IRB, and ethics committees to inspect all study-related documents and pertinent medical records for confirmation of data contained within the eCRFs.

Syneos Health will be responsible for activities associated with the Statistical Analysis Plan and for data management of this study. This will include producing an eCRF and setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and production of queries.

Automated checks will be made against the data to ensure completeness and consistency. The database and check programs will be validated prior to implementation. Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications in the database will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

17. STATISTICAL ANALYSIS

Further details of the planned statistical analysis will be provided in the Statistical Analysis Plan.

17.1 DETERMINATION OF SAMPLE SIZE

Eligible patients will be enrolled equally in a randomization ratio 1:1 (piromelatine 20 mg and placebo).

Assuming an effect size between treatment dose and placebo of 0.51 over 26 weeks in ADAS-Cog14 for participants who are 2:107,510,000-107,540,000 polymorphism non-carriers, a significant level (α) of 0.05, and power of 90%, a sample size of 83 patients/arm is calculated.

Assuming a 25% screen failure rate and 25% 2:107,510,000-107,540,000 polymorphism carriers, 400 patients should be screened in order to randomly assign 225 participants. Assuming 26% withdrawal, 166 patients are expected to complete the 26 weeks study. Allowing for another 24% patient withdrawal during the open-label long term study, 126 patients will complete the 80 weeks period.

17.2 POPULATIONS FOR ANALYSIS

All patients randomized to treatment who have taken at least 1 dose of study medication will be included in the safety analysis set for the evaluation of safety.

The evaluation of efficacy will be based on 2 analysis sets, the full analysis set and the per-protocol set. The full analysis set is the primary population and will include all patients in the safety analysis set who satisfy all entry criteria and who have efficacy data for the primary parameter recorded for baseline and at least 1 postbaseline period assessment. The per-protocol set will include all patients in the full analysis set who have no major protocol violations.

17.3 ANALYTICAL MEASURES

Statistical testing will be two-tailed at the 5% level of significance.

17.3.1 Analysis of Demographics and Baseline Characteristics

Demographic data (age, gender, BMI), education (years), duration of AD, severity of disease as expressed by MMSE score, β-amyloid 42/40 and ApoE4 genotyping will be summarized by treatment group for the full analysis set using descriptive statistics.

Prior medication, compliance, and medical and surgical history will be summarized by treatment group for the full analysis set using descriptive statistics.

No formal statistical testing will be performed on these data.

17.3.2 Analysis of Primary Efficacy Parameter

The ADAS-cog14 score will be summarized at baseline and after 13, and 26 weeks of double-blind treatment (actual and change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). The primary efficacy analysis for change from baseline at week 26 will be carried out using an analysis of covariance (ANCOVA) model with

treatment as the main effect, and baseline ADAS-cog14 and APOE genotype as covariates. The primary timepoint is after 26 weeks of double blind treatment.

Secondary efficacy analysis for ADAS-cog14 will be carried out using a mixed model for repeated measures (MMRM) model utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. . The treatment difference estimates at each visit will be reported, with 95% confidence intervals and *P* values For the primary efficacy parameter, the multiple imputation may be used for dealing with missing data.

17.3.3 Analysis of Secondary Efficacy Parameters

All secondary efficacy parameters: ADCS-iADL, ADCS-CGIC, MMSE, NPI and PSQI, will be summarized at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period (actual and change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). MMRM model will also be used to analyze all secondary efficacy endpoints: ADCS-iADL, ADCS-CGIC, MMSE, NPI and PSQI, utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. . The treatment difference estimates at each visit will be reported, with 95% confidence intervals and P values.

For the key efficacy parameter ADCS-iADL, the multiple imputation may be used for dealing with missing data.

The ANCOVA model will also be used to analyze these secondary efficacy endpoints.

17.3.4 Analysis of Exploratory Efficacy Parameters

The following exploratory efficacy parameters will be summarized descriptively:

1. Long-term safety and efficacy of 18 months piromelatine 20 mg compared to end of the double blind period.
2. Disease modifying potential comparing
    a) Difference from baseline in mean ADAS-cog14 scores in the early and delayed start groups by 52 and 78 weeks of treatment.
    b) Difference from baseline in mean MMSE, CDR-SB scores in the early and delayed start groups by 78 weeks of treatment.
    c) Rate of progression in the 26 weeks extension period and the first 26 weeks randomized period for each group (ADAS-cog14, MMSE, ADCS-iADL).

17.3.5 General Considerations

For all ANCOVA and MMRM models, data collected from investigators who enrolled fewer than 6 patients in any 1 treatment group will be combined prior to analysis. If this combination still results in a treatment group having fewer than 6 patients in any 1 treatment group, then this group

of patients will be combined with the next fewest-enrolling investigator. In the event that there is a tie for fewest-enrolling investigator, one of these will be chosen at random by a random-number generator.

The inherent assumption of normally distributed data will be evaluated by generating output for the residuals from the full ANCOVA and MMRM models, which include the interaction term, and by testing for normality using the Shapiro-Wilk test. In the event that the data are predominantly non-normally distributed, analyses will also be conducted on the ranked data. This rank transformation will be applied by ranking all the data for a particular variable, across all investigators and treatments, from lowest to highest. Integer ranks will be assigned starting at 1; mean ranks will be assigned when ties occur.

17.3.6 Analysis of Safety

Descriptive statistics will be provided for AEs, physical examination , change in laboratory parameters, vital signs and ECG. The number of patients taking concomitant medications during the 28-week treatment period (2-week single-blind, placebo run-in period followed by 26-week double-blind, treatment period) will be summarized by WHO drug classification code for each treatment group. The number of patients withdrawing during the treatment periods will be summarized by primary reason for withdrawal for each treatment group.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as AEs that first occur or worsen in severity after the first administration of study medications. The number of patients reporting TEAEs will be summarized during the 28-week treatment period and during the 52 weeks extension period by system organ class and preferred term for each treatment group.

The change in laboratory parameters from baseline (first week of the run-in period) to the end of the 15-week and 28-week treatment periods will be summarized descriptively. The shift tables will also be used showing the number of patients having values below, within, and above the normal range at each assessment for each treatment group separately. Data will not be carried forward for patients withdrawing due to treatment failure.

Physical examination parameters will be summarized as the number of patients who have a normal or abnormal examination at each assessment for each treatment group separately. Data will not be carried forward for patients withdrawing due to treatment failure.

Vital signs and ECG will be summarized at baseline and at the end of the 28-week treatment period (actual and change from baseline) and to the end of 80-week treatment period using descriptive statistics (n, mean, SD, median, minimum, and maximum).

The number of patients withdrawing during the 28-week treatment period and during the 52 weeks extension period will be summarized by primary reason for withdrawal for each treatment group.

No formal statistical testing will be performed on the safety data. These safety parameters will be assessed using the safety analysis set.

17.3.7 Subgroup Analysis

The effect of age, gender, origin, baseline disease severity as measured by MMSE, ApoE4, Amyloid Probability Score (APS), baseline insomnia severity, and patient education level upon

efficacy will be evaluated if sample sizes are sufficient to warrant such analyses. For example, if all patients are Caucasian, then there is no need to evaluate the co-factor origin. The ANCOVA and MMRM models described above will be supplemented with terms for the main effect and interaction with treatment. Each co-factor will be analyzed in separate models. The test for treatment-by-subgroup interaction will address whether the response to piromelatine, compared with placebo, is different or consistent between levels of the co-factor.

18. INSTITUTIONAL REVIEW BOARD APPROVAL

This study will be conducted in accordance with the provisions of the Declaration of Helsinki (latest revision, Fortaleza 2013). In addition, this study will be undertaken in accordance with the protocol and GCP on the conducting and monitoring of clinical studies. The IRB must be constituted according to the International Council for Harmonization (ICH) guidelines on GCP and local laws.

The investigator will submit the protocol, patient information, and consent forms to the local and/or central IRB through Syneos Health and its written unconditional approval will be obtained and submitted to the sponsor before the start of the study.

Neurim Pharmaceuticals will ensure an investigator's brochure is available. The investigator will submit the investigator's brochure and protocol to the IRB through Syneos Health for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol and patient information and consent forms will be transmitted to Syneos Health and thence to Neurim Pharmaceuticals, prior to the start of the study. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review.

The IRB must be informed by the investigator through Syneos Health of all subsequent protocol amendments and of unexpected SAEs occurring during the study, which are likely to affect the safety of the patients or the conduct of the study.

The investigator should provide the IRB with all relevant amendments or updates of the protocol and investigator's brochure through Syneos Health. Also, the investigator should provide written reports to the IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the patients. A final report of study outcome, if required, should also be submitted by the investigator through Syneos Health to the IRB.

19. INFORMED CONSENT

The principles of informed consent in the Declaration of Helsinki and Guidelines on GCP should be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB. Patients and/or their relatives must be given ample opportunity to inquire about details of the study. The patient must be capable to sign the consent form as judged by the study investigator. The legal representative will be allowed to sign only as dictated by local legal circumstances.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and Guidelines on GCP and will also comply with local regulations. Consent forms must be in a language fully comprehensible to the prospective patient. Informed consent will be documented by the use of a written consent form approved by the IRB and signed by the patient and the investigator obtaining the consent. The ICF will also be annotated with the study patient or screening number. The signature confirms the consent is based on information that has been understood. Each patient's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Neurim Pharmaceuticals, or Syneos Health.

The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel to have access to source data which support the data on the eCRF (e.g., medical records, appointment books, original laboratory records). These personnel will not disclose any of the patient's personal medical information.

Each informant will be given an informed consent form (ICF) to read and sign. This ICF will comply with the Declaration of Helsinki and Guidelines on GCP, as well as local regulations. Informed consent forms must be in a language fully comprehensible to the prospective informant. Informed consent will be documented by the use of a written information sheet approved by the IRB and signed by the informant. The signature confirms the consent is based on information that has been understood. Each informant's signed information sheet must be kept on file by the investigator for possible inspection by regulatory authorities, Neurim Pharmaceuticals, or Syneos Health personnel.

20. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

To ensure both the safety of participants in the study, and the collection of accurate, complete, and reliable data, Neurim Pharmaceuticals or its representatives will perform the following activities:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the clinical report forms, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate clinical report form data and use standard computer edits to detect errors in data collection.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will do the following:

- Keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.

Neurim Pharmaceuticals or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Neurim Pharmaceuticals and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

21. RECORDS AND SUPPLIES

21.1 DRUG ACCOUNTABILITY

Upon receipt of study medication, the investigator (or investigator's designee) will conduct an inventory of the supplies and complete a supplies receipt. The investigator will retain a copy of this receipt at the site and return the original receipt to the study monitor.

It is the responsibility of the study monitor to ensure that the investigator (or investigator's designee) has correctly documented the dispensing and return of study medication on the dispensing log, which will be provided. The study monitor will arrange regular collection of unused study medication returned by the patient. The study monitor will also perform an inventory of study medication at the close-out visit to the site. All discrepancies must be accounted for and documented.

21.2 ELECTRONIC CASE REPORT FORMS

In accordance with GCP and ICH Guidelines, the study monitor will carry out source document verification to ensure that the data collected in the eCRF are accurate and reliable. Source document verification involves cross-referencing data in the eCRF with those recorded in any source document (e.g., patients' medical notes, nurses' notes, appointment diaries, laboratory reports).

All key trial information must be recorded in the patient's medical notes. This includes confirmation of diagnosis, date of informed consent given and of study entry, visit dates, start and stop dates of study medication, changes to concomitant medication, and AEs. Study procedures will be fully documented in the eCRFs and signed by the investigator. For data required to be transcribed into the eCRF, a check on accuracy will be performed by the investigator. The investigator will check relevant laboratory reports for accuracy, will annotate the laboratory report for values of clinical significance and out of range values, and then will sign and date such reports.

21.3 CRITICAL DOCUMENTS

The investigator must permit the monitor, the sponsor's internal auditors, IRB, independent ethics committees, and representatives from the regulatory authorities to have direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

21.4 INSURANCE

Insurance for this study will be arranged and financed by the sponsor of the study according to applicable laws.

21.5 INVESTIGATOR INFORMATION

The name, title, and institution of the investigators are to be listed on the "Investigator" page provided in Section 2 of this protocol. If the investigator is changed after the study has been approved by an IRB, or a regulatory agency, or by Neurim Pharmaceuticals, this addition will not

be considered a change to the protocol. However, the "Investigator" page will be updated to provide the new information.

21.6 FINAL REPORT SIGNATURE

The study chair will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The investigator who will serve as the study chair will be named by the sponsor of the study.

22. REPORTING AND PUBLICATION, INCLUDING RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or their representatives. Essential documents must be retained for 2 years after the final marketing approval in an ICH region or at least 2 years have elapsed since the discontinuation of clinical development of the investigational product. The investigator must contact the sponsor before destroying any trial-related documentation. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

Neurim Pharmaceuticals has the ownership of all data and results collected during this study. In consequence, Neurim Pharmaceuticals reserves the right to use the data of the present study, either in the form of eCRFs (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country. Furthermore, in the event that the clinical research leads to patentable results, the investigator (or entity acting on his behalf following local requirements) shall refrain from filing patent(s) application which will be filed by Neurim Pharmaceuticals, or any other entity delegated by Neurim Pharmaceuticals.

Presentations and/or publications will be considered as joint scientific efforts between the investigators, Syneos Health, and Neurim Pharmaceuticals. They will be prepared and signed by authors of each party.

23. APPENDIX 1

ALCOHOL EQUIVALENTS

Average degrees of alcohol (in grams of alcohol) in the most commonly found drinks:

Drinks	Degrees	Volume (mL)
Beer (draught)	3-4	250
Beer (bottled)	5-6	250 or 330
Cider	5-6	200-250 (1 glass)
Wine	10-12	100-150 (glass)
Fortified wine	18-20	50
Pastis	45	25
Whisky	10-45	25
Strong liqueurs	40-60	25

* Alcohol consumption in mL = degrees × volume (mL) ÷ 100

* Alcohol consumption in g = alcohol consumption (mL) × 0.8

24. APPENDIX 2

PROHIBITED AND RESTRICTED MEDICATIONS

The washout window for prohibited medications is 5 days or 5 half-lives, whichever is longer, after ICF signature.

Drug Category	Drug Subcategory	Medication-PT	Status
Immunoglobulin gamma 1 (IgG1) monoclonal antibody	Amyloid beta-directed antibody	Aducanumab	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Atropine	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Benztropine	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Benztropine Mesilate	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Biperiden	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Chlorpheniramine	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Diphenhydramine	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Diphenhydramine Hydrochloride	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Ipratropium	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Ipratropium Bromide	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Orphenadrine	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Oxitropium	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Tolterodine	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Tiotropium	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Tiotropium Bromide	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Trihexyphenidyl	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Trihexyphenidyl Hydrochloride	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Scopolamine	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Nicotinic agents	Dextromethorphan	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Nicotinic agents	Dextromethorphan Hydrobromide	PROHIBITED
ANTICHOLINERGIC AGENTS	Anti-Nicotinic agents	Dextromethorphan W/Paracetamol/ Phenylephrine	PROHIBITED
NOOTROPIC SUPPLEMENT	AchEI	Huperzine	Prohibited (added 25 Nov 2015)
ANTIDEPRESSANTS	Other (NaSSA)	Mirtazapine	PROHIBITED
ANTIDEPRESSANTS	Other (NRIs)	Atomoxetine	Prohibited even if not formally a CNS stimulant
ANTIDEPRESSANTS	Other (NS)	Agomelatine	Prohibited (revised 25 Nov 2015)
ANTIDEPRESSANTS	Other (SARIs)	Trazodone	PROHIBITED
ANTIDEPRESSANTS	Other (SARIs)	Trazodone Hydrochloride	PROHIBITED
ANTIDEPRESSANTS	Other (SSRIs)	Fluvoxamine	PROHIBITED
ANTIDEPRESSANTS	Other (SSRIs)	Fluvoxamine Maleate	PROHIBITED
ANTIDEPRESSANTS	Other (TAAR1 agonists)	Amphetamine	PROHIBITED
ANTIDEPRESSANTS	Other (TAAR1 agonists)	Dextroamphetamine	PROHIBITED
ANTIDEPRESSANTS	Other (TAAR1 agonists)	Dextromethampheta-mine	PROHIBITED
ANTIDEPRESSANTS	Other (TAAR1 agonists)	Lisdexamfetamine	PROHIBITED
ANTIDEPRESSANTS	Other (TeCAs)	Amoxapine	PROHIBITED
ANTIDEPRESSANTS	Other (TeCAs)	Mirtazapine	PROHIBITED
ANTIDEPRESSANTS	MAOI (Irreversible)	Isocarboxazid	PROHIBITED
ANTIDEPRESSANTS	MAOI (Irreversible)	Phenelzine	PROHIBITED
ANTIDEPRESSANTS	MAOI (Irreversible)	Selegiline	PROHIBITED
ANTIDEPRESSANTS	MAOI (Irreversible)	Tranylcypromine	PROHIBITED
ANTIDEPRESSANTS	MAOI (Reversible)	Moclobemide	PROHIBITED
ANTIDEPRESSANTS	MAOI (Reversible)	Pirlindole	PROHIBITED
ANTIDEPRESSANTS	MAOI (Reversible)	Pirazidol	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
ANTIDEPRESSANTS	SSRIs	Sertraline, Paroxetine, Fluoxetine	RESTRICTED (must be under stable dose for at least 3 months prior to screening)
ANTIDEPRESSANTS	SNRIs	Venlafaxine, Duloxetine	RESTRICTED (must be under stable dose for at least 3 months prior to screening)
ANTIDEPRESSANTS	Dopamine/ Norepinephrine RIs	Bupropion hydrochloride	Prohibited (revised 25 Nov 2015)
ANTIDEPRESSANTS	Tricyclic antidepressants	Amitriptyline	PROHIBITED
ANTIDEPRESSANTS	Tricyclic antidepressants	Amitriptyline Hydrochloride	PROHIBITED (TAC with high sedative/ anticholinergic action)
ANTIDEPRESSANTS	Tricyclic antidepressants	Amitriptylinoxide	PROHIBITED (TAC with high sedative/ anticholinergic action)
ANTIDEPRESSANTS	Tricyclic antidepressants	Clomipramine	PROHIBITED (TAC with high sedative/ anticholinergic action)
ANTIDEPRESSANTS	Tricyclic antidepressants	Clomipramine Hydrochloride	PROHIBITED (TAC with high sedative/ anticholinergic action)
ANTIDEPRESSANTS	Tricyclic antidepressants	Doxepin	PROHIBITED (TAC with high sedative/ anticholinergic action)

Drug Category	Drug Subcategory	Medication-PT	Status
ANTIDEPRESSANTS	Tricyclic antidepressants	Nortriptyline	RESTRICTED (must be under stable dose for at least 3 months prior to screening)
ATYPICAL ANTIPSYCHOTICS +	Combination products	Olanzapine/Fluoxetine	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Aripiprazole	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Asenapine	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Asenapine Maleate	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Iloperidone	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Olanzapine	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Olanzapine Embonate	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Paliperidone	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Paliperidone Palmitate	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Quetiapine	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Quetiapine Fumarate	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Risperidone	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Ziprasidone	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Ziprasidone Hydrochloride	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Lurasidone	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Lurasidone Hydrochloride	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Zotepine	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
ATYPICAL ANTIPSYCHOTICS	Atypical	Amisulpride	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Sulpiride	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Clozapine	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Bifeprunox	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Brexpiprazole	PROHIBITED
ANXIOLITICS	Benzodiazepines	Alprazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Bretazenil	PROHIBITED
ANXIOLITICS	Benzodiazepines	Bromazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Brotizolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Chlordiazepoxide	PROHIBITED
ANXIOLITICS	Benzodiazepines	Cinolazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Clonazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Clorazepate	PROHIBITED
ANXIOLITICS	Benzodiazepines	Clotiazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Cloxazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Delorazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Diazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Estazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Etizolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Flunitrazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Flurazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Flurazepam Hydrochloride	PROHIBITED
ANXIOLITICS	Benzodiazepines	Flutoprazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Halazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Ketazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Loprazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Lorazepam and other medium-acting benzodiazepines	Prohibited in regular dose prior to screening. Restricted as per protocol section 12.9.1 Rescue Medication during trial

Drug Category	Drug Subcategory	Medication-PT	Status
ANXIOLITICS	Benzodiazepines	Lormetazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Medazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Midazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Midazolam Hydrochloride	PROHIBITED
ANXIOLITICS	Benzodiazepines	Midazolam Maleate	PROHIBITED
ANXIOLITICS	Benzodiazepines	Nimetazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Nitrazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Nordazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Oxazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Phenazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Pinazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Prazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Premazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Pyrazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Quazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Temazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Tetrazepam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Triazolam	PROHIBITED
ANXIOLITICS	Benzodiazepines	Clobazam	PROHIBITED
ANXIOLITICS	Benzodiazepines	DMCM	PROHIBITED
HYPNOTICS	Z- drugs	Eszopiclone	PROHIBITED
HYPNOTICS	Z- drugs	Zaleplon	PROHIBITED
HYPNOTICS	Z- drugs	Zolpidem	PROHIBITED
HYPNOTICS	Z- drugs	Zolpidem Tartrate	PROHIBITED
HYPNOTICS	Z- drugs	Zopiclone	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Adderall	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Obetrol	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Amphetamine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Dexmethylphenidate	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Dextroamphetamine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Dextromethampheta-mine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Lisdexamfetamine	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
CNS STIMULANTS	Substituted phenethylamines	Methylphenidate	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Methylphenidate hydrochloride	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Mixed amphetamine salts	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Benzedrine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Bupropion	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Bupropion hydrochloride	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Cathinone	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Ecstasy	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Methamphetamine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Ephedrine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	MDMA	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	MDPV	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Caffeine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Catha edulis	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Cocaine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Khat	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Mephedrone	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Methylenedioxypyro-valerone	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Methylone	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Phenylpropanolamine	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
CNS STIMULANTS	Substituted phenethylamines	Propylhexadrine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Pseudoephedrine	PROHIBITED
CNS STIMULANTS	Substituted phenethylamines	Pseudoephedrine Hydrochloride	PROHIBITED
CNS STIMULANTS	Eugeroics	Adrafinil	PROHIBITED
CNS STIMULANTS	Eugeroics	Armodafinil	PROHIBITED
CNS STIMULANTS	Eugeroics	Modafinil	PROHIBITED
CNS STIMULANTS	Nicotine therapy	Varenicline tartrate	PROHIBITED
INSULIN REPLACEMENT THERAPY	Insulin and analogs	Insulin (any source), Lispro,Aspart,Degludec+Aspart, combinations	PROHIBITED
IMMUNOSUPPRESSANTS	CORTICOSTEROIDS (at immunosuppresive dose)	Prednisone	PROHIBITED
IMMUNOSUPPRESSANTS	CORTICOSTEROIDS (at immunosuppresive dose)	Prednisolone	PROHIBITED
IMMUNOSUPPRESSANTS	CORTICOSTEROIDS (at immunosuppresive dose)	Dexamethasone	PROHIBITED
IMMUNOSUPPRESSANTS	CYTOTOXIC AGENTS	Cyclophosphamide	PROHIBITED
IMMUNOSUPPRESSANTS	CYTOTOXIC AGENTS	Methotrexate	PROHIBITED
IMMUNOSUPPRESSANTS	CYTOTOXIC AGENTS	Azathiprine	PROHIBITED
IMMUNOSUPPRESSANTS	T-CELL SUPPRESIVE AGENTS	Cyclosporine	PROHIBITED
IMMUNOSUPPRESSANTS	T-CELL SUPPRESIVE AGENTS	Tacrolimus	PROHIBITED
Melatonin agonists	melatonin receptor agonists	Melatonin,Ramelteon	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Carbamazepine	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Divalproex sodium	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Lamotrigine	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Oxcarbazepine	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Sodium valproate	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
MOOD STABILIZERS	ANTIEPILEPTICS	Valproate sodium	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Valproate magnesium	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Valproate semisodium	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Topiramate	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Acetazolamide	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Valproic acid	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Primadone	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Phenytoin	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Ergenyl chrono	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Phenobarbital	PROHIBITED
MOOD STABILIZERS	MINERAL	Lithium	PROHIBITED
MOOD STABILIZERS	ANTIEPILEPTICS	Gabapentin	PROHIBITED
MOOD STABILIZERS	MINERAL	Lithium carbonate	PROHIBITED
DIETARY SUPPLEMENTS	NUTRACEUTICALS	Souvenaid, DHA [DOCOSAHEXAENOIC ACID], Phosphatidylserine, Omega-3, Ginkgo biloba, Ginseng, Huperzia serrata, Vitamin B, Vitamin D, Vitamin E	RESTRICTED (must be under stable dose for at least 3 months prior to screening)
OPIOIDS	Allosteric modulators	Cannabidiol	PROHIBITED
OPIOIDS	Allosteric modulators	Tetrahydrocannabinol	PROHIBITED
OPIOIDS	Benzomorphan derivatives	Dezocine	PROHIBITED
OPIOIDS	Benzomorphan derivatives	Pentazocine	PROHIBITED
OPIOIDS	Benzomorphan derivatives	Phenazocine	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Bezitramide	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Dextromoramide	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Dextropropoxyphene	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Difenoxin	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Diphenoxylate	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Dipipanone	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	LAAM	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
OPIOIDS	Diphenylpropylamine derivatives	Levomethadyl Acetate	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Loperamide	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Methadone	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Piritramide	PROHIBITED
OPIOIDS	Diphenylpropylamine derivatives	Propoxyphene	PROHIBITED
OPIOIDS	Esters of morphine	Acetylpropionyl-morphine	PROHIBITED
OPIOIDS	Esters of morphine	Desomorphine	PROHIBITED
OPIOIDS	Esters of morphine	Diacetyldihydro-morphine	PROHIBITED
OPIOIDS	Esters of morphine	Diacetylmorphine	PROHIBITED
OPIOIDS	Esters of morphine	Dibenzoylmorphine	PROHIBITED
OPIOIDS	Esters of morphine	Dipropanoylmorphine	PROHIBITED
OPIOIDS	Esters of morphine	Heroin	PROHIBITED
OPIOIDS	Esters of morphine	Methyldesorphine	PROHIBITED
OPIOIDS	Esters of morphine	Morphine diacetate	PROHIBITED
OPIOIDS	Esters of morphine	Morphine dinicotinate	PROHIBITED
OPIOIDS	Esters of morphine	Morphine dipropionate	PROHIBITED
OPIOIDS	Esters of morphine	Morphine sulfate	PROHIBITED
OPIOIDS	Esters of morphine	Nicomorphine	PROHIBITED
OPIOIDS	Ethers of morphine	Dihydrocodeine	PROHIBITED
OPIOIDS	Ethers of morphine	Ethylmorphine	PROHIBITED
OPIOIDS	Ethers of morphine	Heterocodeine	PROHIBITED
OPIOIDS	Morphinan derivatives	Butorphanol	PROHIBITED
OPIOIDS	Morphinan derivatives	Levomethorphan	PROHIBITED
OPIOIDS	Morphinan derivatives	Levorphanol	PROHIBITED
OPIOIDS	Morphinan derivatives	Nalbuphine	PROHIBITED
OPIOIDS	Opioid antagonists:	Nalmefene	PROHIBITED
OPIOIDS	Opioid antagonists:	Naloxone	PROHIBITED
OPIOIDS	Opioid antagonists:	Naltrexone	PROHIBITED
OPIOIDS	Opium alkaloids	Codeine	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
OPIOIDS	Opium alkaloids	Morphine	PROHIBITED
OPIOIDS	Opium alkaloids	Oripavine	PROHIBITED
OPIOIDS	Opium alkaloids	Papaveretum	PROHIBITED
OPIOIDS	Opium alkaloids	Thebaine	PROHIBITED
OPIOIDS	Oripavine derivatives	Buprenorphine	PROHIBITED
OPIOIDS	Oripavine derivatives	Dihydroetorphine	PROHIBITED
OPIOIDS	Oripavine derivatives	Etorphine	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Buprenorphine	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Etorphine	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Hydrocodone	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Hydromorphone	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Hydromorphone Hydrochloride	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Vicodin	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Oxycocet	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Oxycodone	PROHIBITED
OPIOIDS	Semi-synthetic alkaloid derivatives	Oxymorphone	PROHIBITED
OPIOIDS	Synthetic opioids: Anilidopiperidines	Alfentanil	PROHIBITED
OPIOIDS	Synthetic opioids: Anilidopiperidines	Alphamethylfentanyl	PROHIBITED
OPIOIDS	Synthetic opioids: Anilidopiperidines	Carfentanyl	PROHIBITED
OPIOIDS	Synthetic opioids: Anilidopiperidines	Fentanyl	PROHIBITED
OPIOIDS	Synthetic opioids: Anilidopiperidines	Ohmefentanyl	PROHIBITED
OPIOIDS	Synthetic opioids: Anilidopiperidines	Remifentanil	PROHIBITED
OPIOIDS	Synthetic opioids: Anilidopiperidines	Sufentanil	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	Allylprodine	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
OPIOIDS	Synthetic opioids: Phenylpiperidines	Ketobemidone	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	meperidine	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	MPPP	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	PEPAP	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	Pethidine	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	Prodine	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	Panadeine CO	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	Nuprofen Plus	PROHIBITED
OPIOIDS	Synthetic opioids: Phenylpiperidines	Nembudeine	PROHIBITED
OPIOIDS	Other	Tapentadol	PROHIBITED
OPIOIDS	Other	Tramadol	PROHIBITED
OPIOIDS	Other	Tramadol Hydrochloride	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Chlorpromazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Chlorpromazine Hydrochloride	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Chlorprothixene	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Clopenthixol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Cyamemazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Dixyrazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Flupentixol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Flupentixol Decanoate	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Fluphenazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Fluphenazine Hydrochloride	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Fluphenazine Decanoate	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Levomepromazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Levomepromazine Maleate	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Mesoridazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Perazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Perazine Dunakinate	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Pericyazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Perphenazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Pipotiazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Prochlorperazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Promazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Promethazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Prothipendyl	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Thioproperazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Thioridazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Thioxanthenes	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Tiotixene	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Trifluoperazine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Trifluoperazine Hydrochloride	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Triflupromazine	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Zuclopenthixol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Zuclopenthixol Acetate	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Phenothiazines	Zuclopenthixol Decanoate	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Benperidol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Bromperidol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Diphenylbutylpiper-idine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Droperidol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Fluspirilene	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Haloperidol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Haloperidol Decanoate	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Moperone	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Penfluridol	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Pimozide	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Pipamperone	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Pipamperone Hydrochloride	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Butyrophenones	Timiperone	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Conventional	Clotiapine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Conventional	Loxapine	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Neuroleptic	Tiapride	PROHIBITED
TYPICAL ANTIPSYCHOTICS	Neuroleptic	Sertindole	PROHIBITED

25. APPENDIX 3

Clinically significant comorbid pathologies

MRI / CT Exclusion Criteria:

1. Significant pathological findings on brain MRI / CT at Screening, including but not limited to:

2. An area of superficial siderosis, to be discussed with clinical symptoms;

3. Evidence of cerebral vasogenic edema;

4. Evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions;

5. Evidence of any cortical infarct defined as > 1.5 cm^3

6. Evidence of multiple lacunar infarcts (more than 2 defined as $\leq 1.5\ cm^3$) or single stroke on a major vascular territory,

7. Severe or diffuse white matter disease, Fazekas score of more than 1;

8. Space occupying lesions other than meningiomas or arachnoid cysts less than 1 cm^3

Additional Exclusion Criteria:

1. Lewy body disease, FTD or vascular dementia

2. Head injury with loss of consciousness proximate to the onset of cognitive symptoms

3. Repeated head injuries (eg contact sport) defined as more than 2 concussive events in the 5 year period prior to the first noted memory change

4. Patients who have been diagnosed with an Axis 1 disorder (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision [DSM-5] criteria) including, but not limited to:

   - Schizophrenia, schizoaffective disorder, or other psychotic disorders not related to dementia

   - Bipolar I or II disorder, bipolar disorder not otherwise specified

   - Current Major Depressive Episode: Patients with a history of major depressive disorder, that is currently not symptomatic, are eligible. Patients currently on a stable

dose(s) of allowed antidepressant medication(s) for at least 3 months prior to the Screening visit are eligible (see Appendix 2)

5. Patients with any known use of illegal substances within the 12 months prior to Screening and/or a history of substance and/or alcohol use disorder within 2 years prior to Screening.

6. Transient ischemic attacks (TIA) or stroke within 12 months of Screening

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