Neurim Pharmaceuticals (1991) Ltd
27 Habarzel Street
Tel-Aviv 69710
ISRAEL

NCT02615002

STUDY NUMBER: NEUP11-AD2

RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED, DOSE-RANGING STUDY OF PIROMELATINE IN PATIENTS WITH MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE

PHASE: 2

CONFIDENTIAL

CRO:	INC Research, LLC 3201 Beechleaf Court, Suite 600 Raleigh, North Carolina 27604 USA
DATE OF PROTOCOL:	Version 1, 23 July 2015
STATUS OF PROTOCOL:	Final Version 7, 10 April 2017

2. APPROVAL SIGNATURES

RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED, DOSE-RANGING STUDY OF PIROMELATINE IN PATIENTS WITH MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE

Protocol No. NEUP11-AD2

NEURIM PHARMACEUTICALS (1991) LTD

April 12, 2017

_____ Date: _____

Amnon Katz, PhD
VP, Clinical Development
Neurim Pharmaceuticals (1991) Ltd
27 Habarzel Street
Tel-Aviv 69710
ISRAEL

SPONSOR'S SAFETY OFFICER

_____ Date: 12th April 2017

Tali Nir, DVM
VP, Clinical and Regulatory Affairs
Neurim Pharmaceuticals (1991) Ltd
27 Habarzel Street
Tel-Aviv 69710
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.

	Amnon Katz, PhD
_____	_____
Principal Investigator	Sponsor Representative
	
_____	_____
Signature	Signature
	April 12, 2017
_____	_____
Date	Date

_____

Name of Site

3. SUMMARY/SYNOPSIS OF PROTOCOL

STUDY NUMBER	NEUP11-AD2
STUDY DRUGS **Test drug** **Control drug**	 Piromelatine 5, 20, and 50 mg tablets Matched placebo tablets
TITLE	Randomized, Double-blind, Parallel-group, Placebo-controlled, Dose-ranging Study of Piromelatine in Patients with Mild Dementia Due to Alzheimer's Disease
STUDY PHASE	2
COUNTRIES	United States
ESTIMATED NUMBER OF CENTERS	Approximately 75 sites
STUDY RATIONALE	Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the leading cause of dementia in the elderly population. People progressing to AD develop distressing changes in memory, thought, function, and behavior, which worsen over time. These changes increasingly impact the person's daily life and reduce their independence until ultimately these patients are entirely dependent on others (Querfurth and LaFerla, 2010). Worldwide, it is estimated that about 36 million people have dementia. Alzheimer's disease accounts for 50% to 80% of these patients (Duthey, 2013). At early-stage AD, the episodic memory is the most noticeable impairment (Gold and Budson, 2008). With the shift towards an increasingly elderly population, it is predicted that the number of people affected by early-stage AD that will progress to dementia will almost double every 20 years, and by the year 2050, 115 million people will have the condition (Duthey, 2013). 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 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 hallmark pathological feature of AD is the presence of brain

	plaques, consisting primarily of β-amyloid peptide (Aβ) aggregates (Selkoe, 2002). Accordingly, the abnormal production and aggregation of Aβ, associated particularly with late-stage disease, has been the principal target of many drug development efforts. However, 3 trials of Aβ lowering agents involving patients with overt dementia failed to show improvements in cognition. A leading theory posits that the attempts at intervention may have been made too late in the progression of disease, at a stage when neuronal damage had become too widespread, and therefore more trials now focus on patients in whom overt dementia seems imminent. An ideal drug for such patients will improve neuropsychological performance and functional abilities, slow down Aβ buildup, and promote neuroprotection and neurogenesis. 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. Through this unique molecular mode of action, piromelatine demonstrated in preclinical studies in rodents neuroprotective (Buendia et al., 2014, Tang et al., 2012), memory enhancing (He et al., 2013, Tian et al., 2010), sleep promoting (Liu et al., 2014), and neurogeneration enhancing capabilities (Tian et al., 2015 unpublished) with relevance to AD risk factors, comorbidities, and symptoms. The 5HT-1a agonists have demonstrated neuroprotective effects (Kline et al., 2004) by increasing both cell proliferation and neurogenesis in the hippocampal subgranular zone of the dentate gyrus and the subventricular zone (Banasr et al., 2004, Islam et al., 2014) and increase slow wave sleep (SWS) specifically by inhibition of hypothalamic orexin neurons and the dorsal raphe nuclei that act as wake promoting centers (Muraki et al., 2004, Tabuchi et al., 2013). Simultaneous activation of melatonergic and 5HT-1a receptors may synergistically promote neurogenesis (Fava et al., 2012). The sleep enhancing capacities of piromelatine may also be relevant to the therapeutic potential. Recent clinical and biochemical evidence has identified an interesting link between sleep, Aβ, cognitive dysfunction, and AD. In mice, Aβ clearance through the glymphatic system (the biomolecule clearance system operating the convective flow between the cerebrospinal fluid [CSF] and interstitial fluid to remove toxic metabolites) is strongly stimulated by sleep (Mendelsohn and Larrick, 2013, Xie et al., 2013). Bidirectional relationships between sleep and Aβ production have been demonstrated in mice overexpressing Aβ (Roh et al., 2012). In humans, normal soluble Aβ concentrations in the CSF fluctuate with the sleep-wake cycle with 6 hours delay (Huang et al., 2012). Disruption of non-rapid eye movement (NREM) SWS resulted in impaired overnight consolidation of long-term memory in healthy older adults (Mander et al., 2015). Since Aβ production is highest at times of neural activity such as during wakefulness and lowest at times of decreased neural activity such as during SWS, sleep

	disturbances accompanied by loss of SWS may lead to an increase in production of soluble CSF Aβ, increased Aβ aggregation, and attenuation of the Aβ diurnal pattern characterizing AD (Lucey and Bateman, 2014). Bidirectional relations between Aβ pathology and NREM sleep physiology were observed also in patients with mild cognitive impairment (MCI) and AD. In MCI patients the reduction in SWS was associated with deficits in sleep dependent memory consolidation (Pace-Schott and Spencer, 2015). Moreover, MCI patients had modified sleep structure characterized by shorter and disrupted SWS and lower Δ and Θ power as compared to controls (Westerberg et al., 2012). In AD patients, higher SWS was positively associated with retrieval of recent autobiographical memories (Rauchs et al., 2013). Indeed, 63% of the patients with subtle cognitive deficits (also termed MCIs) (McKinnon et al., 2014) and 44% of the patients diagnosed with AD (Vitiello and Borson, 2001) demonstrate sleep disturbances as determined using the Pittsburgh Sleep Quality Index (PSQI). More recently, neuropathological analyses revealed a positive correlation between total sleep time, sleep quality, and sleep onset latency in demented and nondemented older adults with higher Aβ burden in specific brain areas that are linked to early AD (Spira et al., 2013). Accordingly, deterioration in cognition from healthy controls through MCI to AD patients was associated with parallel deterioration in sleep (Economou et al., 2013). The presence of insomnia may thus help identify patients with early signs of AD who are at a greater risk of deteriorating to dementia. The relation becomes evident as poor sleep is directly associated with cognitive decline in healthy (Miyata et al., 2013) cognitively impaired (McKinnon et al., 2014) and demented adult populations (Vitiello et al., 1990), including AD (Carpenter et al., 1996, McCurry et al., 1999). Further exploration of interventions that promote NREM SWS and minimize the progression of neurodegeneration and the cognitive dysfunction associated with Aβ pathology is needed (Mander et al., 2015). Importantly, the mechanism of sleep induction appears to be of key importance for the sought cognitive effects. Long-term use of benzodiazepine is associated with an increased risk of dementia (Billioti de Gage et al., 2012) and AD (Billioti de Gage et al., 2014, Yaffe and Boustani, 2014), presumably because of the known suppression of NREM SWS by benzodiazepines and nonbenzodiazepine hypnotics (Arbon et al., 2015). Treatment of patients with AD suffering from sleep disturbances with traditional hypnotics is associated with increased risk for a wide range of injuries (Chung et al., 2013, Diem et al., 2014) and may actually worsen their cognition and memory (Hall-Porter et al., 2014). In contrast, melatonin receptor agonism, which maintains the NREM SWS (Arbon et al., 2015), appears beneficial for cognition and functioning in mild to moderate AD patients (Wade et al., 2014). 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 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 suggested dose-dependent beneficial effects of piromelatine on sleep continuity measures. 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 et al., 2012). In a Phase 2, randomized, placebo-controlled, sleep laboratory study in insomnia patients (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). 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 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. Altogether, through its action at melatonin receptors, piromelatine may improve sleep, circadian rhythms control, and, subsequently, cognition in the patients (Wade et al., 2014). Through the serotonergic mechanism, piromelatine may improve memory and mood (Rodríguez et al., 2012), enhance SWS, and reduce wakefulness (Bjorvatn and Ursin, 1998, Monti and Monti, 2000). Through the combined activation of melatonergic and 5HT-1a receptors, piromelatine may act synergistically to increase neurogenesis (Fava et al., 2012). This study is a Phase 2, randomized, placebo-controlled, dose-ranging study of piromelatine (5, 20, and 50 mg daily for 6 months) versus placebo to determine an effective dose to take forward to Phase 3 studies based on efficacy (cognitive performance), safety, and tolerability in patients with mild dementia due to AD.
PRIMARY OBJECTIVE	1. To compare the effect of piromelatine (5, 20, and 50 mg) to

	that of placebo in the change from baseline in global composite score of the computerized Neuropsychological Test Battery (cNTB) after 26 weeks of double-blind treatment The global composite score includes the International Shopping List Test (ISLT; immediate and delayed recall), One Card Learning (OCL), Identification, Detection, and One Back Card (OBK).
KEY SECONDARY OBJECTIVES	1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on global impression assessed by the Clinical Global Impression of Change (CGIC) after 26 weeks of double-blind treatment 2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients (ADCS-MCI-ADL) at Weeks 13 and 26 and over 26 weeks of double-blind treatment
OTHER SECONDARY OBJECTIVES	1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog14) at Weeks 13 and 26 and over 26 weeks of double-blind treatment 2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the change from baseline in global composite score of the cNTB at Weeks 4 and 13 and over 26 weeks of double-blind treatment 3. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the episodic memory domain* composite score of the cNTB at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment * episodic domain tests: ISLT (immediate and delayed recall) and OCL 4. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the attention domain* composite score of the cNTB at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment * attention domain tests: Identification and Detection 5. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the executive function* composite score of the Neuropsychological Test Battery (NTB) at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment * executive function domain tests: OBK, Controlled Oral Word Association Test (COWAT) and Categorical Fluency Test (CFT) 6. To compare the safety and tolerability of piromelatine (5, 20, and 50 mg) to that of placebo
EXPLORATORY	1. To compare the effect of piromelatine (5, 20, and 50 mg) to

OBJECTIVES	that of placebo on cognitive aspects of mental function assessed by the Mini-Mental State Examination (MMSE) after 2 weeks of run-in single-blind placebo followed by 26 weeks of double-blind treatment 2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in individual cNTB test scores (ISLT immediate and delayed recall, OCL, Identification, Detection, OBK) at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment 3. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the change from baseline in behavioral signs and symptoms assessed by the Neuropsychiatric Inventory (NPI) scale after 26 weeks of double-blind treatment 4. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on sleep variables derived from the PSQI at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment 5. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in ADAS-cog13, ADAS-cog12, and ADAS-cog11 score at Weeks 13 and 26 and over 26 weeks of double-blind treatment.
STUDY DESIGN	This is a Phase 2, double-blind, parallel-group, placebo-controlled, dose-ranging safety and efficacy study of piromelatine in patients with mild dementia due to AD. Patients with a documented history of mild dementia due to AD for at least 6 months, having an MMSE score of 20 to 27 (inclusive) at Screening (a score of 27 is allowed only if accompanied by a score of ≥ 12 in the ADAS-cog11 portion of the ADAS-cog14 at Screening), and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1 will be recruited and further screened for eligibility. Caregiver 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 computed tomography (CT) or magnetic resonance imaging (MRI) scan will be obtained to rule out clinically significant comorbid pathologies. 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 1.2:1:1:1 randomization ratio to the 4 trial arms (placebo [1.2], and the equal piromelatine treatment arms 5, 20, and 50 mg [1:1:1]).

	Intermediate visits will be carried out at 4 weeks (Visit 3) and 13 weeks (Visit 4) 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 5 (Week 26) will be brought back for a termination visit. Assuming an effect size between treatment dose and placebo of 0.35 over 26 weeks, a significant level (α) of 0.05, and power of 88%, a sample size of 143 patients for the placebo arm and 119 patients for each of the 3 piromelatine arms is calculated. Assuming a 50% screen failure rate and allowing for 15% patient withdrawal, 1150 patients should be screened in order to randomly assign 575 patients, of whom it is expected 500 will complete the study. Piromelatine (5, 20, and 50 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.
STUDY DURATION	The study consists of a 2-week run-in period of single-blind placebo and a 26-week, randomized, double-blind treatment period comprising administration of piromelatine or placebo, for a total treatment duration of 28 weeks. A follow-up phone call to elicit any safety concerns will be completed 2 weeks after the last dose of study medication.
STUDY POPULATION	Male or female patients diagnosed with mild AD dementia who meet the core clinical research criteria of the NIA-AA (McKhann et al., 2011) These criteria are clinical in nature and 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. Patient has a permanent caregiver (participant's caregiver is not expected to change during the course of the study), who will accompany the patient to the office, and/or be available by telephone at designated times, monitor administration of prescribed medications, control the minimum 2-hour daily light exposure requirement, and be responsible for the overall care of the patient at home. Caregiver must, in the opinion of the investigator, have enough contact with the participant to be able to perform the duties described above. 2. Patient and caregiver are willing to take part in the entire study. 3. Signed informed consent from the patient who is capable to sign the consent form as judged by the study investigator and from the caregiver as dictated by local legal circumstances. 4. Patient is a male or female aged 60-85 years (inclusive). 5. Patient is an outpatient living at home or in an assisted living

	facility with no plans to move or travel during the investigational period. 6. Patient has a clearly documented history either in medical records or from an informant of cognitive decline over at least 6 months. If available, any scale verification of the decline should be requested. 7. Patient has mild probable AD as consistent with criteria established by the NIA-AA (McKhann et al., 2011). 8. Patient has MRI or CT scan, performed within 12 months before Screening, with findings consistent with the diagnosis of dementia due to AD without any other clinically significant comorbid pathologies. If this MRI or CT scan is unavailable or occurred more than 12 months before Screening, this assessment should be completed and the findings confirmed prior to Visit 2 (copy of the report will be available at the study site). 9. Patient has an MMSE score of 20-27 (inclusive) at Screening (a score of 27 is allowed only if accompanied by a score of ≥ 12 in the ADAS-cog11 portion of the ADAS-cog14 at Screening; patients with an MMSE score of 19 may be rescreened once after 1 month). 10. Patient has a CDR-GS of 0.5-1 (mild dementia) at Screening. 11. Patients taking acetylcholinesterase inhibitors 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 agreeable to not starting throughout the study. 13. Patients who stopped receiving acetylcholinesterase inhibitors must be stable off acetylcholinesterase inhibitors for 6 months before Baseline and must be agreeable to not restarting throughout the study. 14. Patient has a negative drug screen (benzodiazepines or opiates) at Screening. 15. Female patients must have had last natural menstruation ≥ 24 months before Screening OR be surgically sterile. 16. 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. 17. 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 or memantine (see Section 12.9) should be on a stable dose for at least 3 months before Screening and throughout the study. 18. Patients who are taking vitamin B12 should be on a stable dose for at least 3 months before Screening and throughout the study. 19. Patient is able to ingest oral medication and participate in all scheduled evaluations. 20. 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). 21. Patient and caregiver have the ability to read and write in English (or Spanish if using Spanish materials) and have hearing, vision, and physical abilities adequate to perform assessments (corrective aids allowed).
EXCLUSION CRITERIA	Potential patients who meet any of the following criteria will be excluded from participating in the study: 1. Patient has an alternative cause for dementia other than AD. 2. A past or recent CT or MRI scan or report indicating brain pathology that is associated with cognitive impairment or incompatible with a diagnosis of probable AD (e.g., any cortical infarct defined as > 1.5 cm^3; more than 2 lacunar infracts defined as ≤ 1.5 cm^3; diffuse white matter disease). The medical monitor should be contacted when there are questions about eligibility. 3. Patient has evidence of any clinically significant neurodegenerative disease, or other serious neurological disorders other than AD, including but not limited to: a) Frontotemporal dementia, dementia with Lewy bodies, or vascular dementia documented by clinical history b) History or presence of any stroke with clinical symptoms ≤ 2 years before Screening c) Epilepsy or history of seizures, except for simple childhood febrile seizures or alcohol withdrawal seizures d) History of clinically relevant head trauma with neurological sequelae e) Parkinson's disease f) Multiple sclerosis g) Amyotrophic lateral sclerosis h) Myasthenia gravis i) Moderate to severe sleep apnea (Apnea Hypopnea Index [AHI] ≥ 15); use of continuous positive airway pressure (CPAP) or other sleep-related devices for sleep apnea j) Narcolepsy 4. Patient has been diagnosed with the following Axis I disorders (Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-V] criteria):

	a) Schizophrenia spectrum and other psychotic disorders (not related to dementia) b) Bipolar and related disorders c) Substance use disorders within the past 2 years 5. Patient has a history of uncontrolled or untreated cardiovascular, endocrine, gastrointestinal, respiratory, or rheumatologic disorders within the past 5 years. 6. Patient has a history of severe agitation. 7. Patient has a known history of human immunodeficiency virus (HIV). 8. Patient has a history of serious infectious disease including: a) Neurosyphilis b) Meningitis c) Encephalitis 9. 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). 10. Patient has severe pain that is likely to interfere with sleep (in the opinion of the investigator). 11. 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 µ3 if due to chronic alcoholism d) Renal failure with creatinine > 150 µmol/L 12. Patient is unable to adequately perform the computerized testing as judged by the study investigator or investigator designee at the practice session during Screening. 13. Continuous use of benzodiazepines or other sedative-hypnotics during the 2 weeks before Screening (see Section 12.9). 14. Patient has a history of chronic use and abuse of benzodiazepines or other sedative-hypnotics. 15. Use of any kind of melatonin/melatonin agonist during the 2 weeks before Screening (see Section 12.9).

	16. Patient has known or suspected hypersensitivity to exogenous melatonin or melatonin receptor agonists. 17. Patient has clinically significant abnormal laboratory findings that have not been approved by the study safety officer. 18. Patient has persistent bradycardia (heart beat < 50 bpm) or tachycardia (heart beat > 100 bpm). 19. 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). 20. Patient has other serious diseases that could interfere with patient assessment, in the opinion of the investigator. 21. Patient has untreated B12 and/or folic acid deficiency. 22. 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. 23. Patient with a body mass index (BMI) above 35 or below 18. 24. 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) 25. Administrative exclusion: a) Patient and/or caregiver unable to contact the investigator by phone in case of an emergency 26. Patients with evidence of serious risk of suicide based on the Sheehan Suicidality Tracking Scale (Sheehan-STS); ie, a score of 3 or 4 on question 2 or 13 and a score of 2 or higher on questions 1a, 3 through 12, and 14 or who, in the opinion of the investigator, present a serious risk of suicide.

EFFICACY PARAMETERS	
Primary parameter	Global composite score of the cNTB
Secondary parameters	- CGIC - ADCS-MCI-ADL - ADAS-cog14 - Global composite score of the cNTB - Episodic memory domain of the cNTB - Attention domain of the cNTB - Executive function domain
Exploratory parameters	- MMSE - cNTB individual scores - NPI - PSQI - ADAS-cog13, ADAS-cog12, and ADAS-cog11
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, Sheehan-STS
PRIMARY EFFICACY STATISTICAL ANALYSIS	The cNTB global composite score (ISLT immediate and delayed recall, OCL, identification, detection, and OBK) will be summarized at baseline and after 4, 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 will be carried out using an analysis of covariance (ANCOVA) model with treatment and study site as the main effects and baseline cNTB global z-score as the covariate. To evaluate the effect of missing cNTB items, multiple imputations will be used for the calculation of cNTB composite scores in the case of 1 or 2 missing cNTB items. Secondary efficacy analyses will be carried out using a mixed-effects maximum likelihood repeated measures (MMRM) model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score as a covariate, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values.
SECONDARY EFFICACY STATISTICAL ANALYSIS	The same aforementioned ANCOVA model will be used to analyze all secondary efficacy endpoints: CGIC, ADCS-MCI-ADL, ADAS-cog14, cNTB global composite score, cNTB episodic memory domain composite score (ISLT and OCL), cNTB attention domain composite score (identification and detection), and executive function composite score (COWAT and CFT). The MMRM model also will be used for the analysis of ADCS-MCI-ADL, cNTB various domains composite score (identification and detection) and executive function

	composite score.
EXPLORATORY EFFICACY STATISTICAL ANALYSIS	The same aforementioned ANCOVA model will be used to analyze the exploratory efficacy endpoints: MMSE, individual cNTB scores, NPI, PSQI (global score and individual components), and ADAS-cog13, ADAS-cog12, and ADAS-cog11 scores. Additionally, the MMRM model will be used for the analysis of individual cNTB scores and the PSQI global and individual component scores.
SAFETY ANALYSIS	Descriptive statistics will be provided for AEs, change in physical examination parameters, and vital signs. 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. The number of patients reporting AEs will be summarized during the 28-week treatment period by body system 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 will be summarized using shift tables 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. The change in physical examination parameters from baseline to the end of the 28-week treatment period 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 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 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: 15 November 2015 Last patient out: 01 March 2019

4. TABLE OF CONTENTS

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 caregiver 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 Harmonisation 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 caregiver 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/caregiver 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 who are willing to participate in the apolipoprotein-E (ApoE4) genotyping will sign a separate applicable ICF.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be a multicenter study conducted in the United States (US).

Study CRO

INC Research, LLC

3201 Beechleaf Court, Suite 600
Raleigh, North Carolina 27604
USA

Study Statistician

INC Research, LLC

Central Laboratory

Covance Central Laboratory Services LP

Safety Officer

Tali Nir, DVM
VP, Clinical and Regulatory Affairs
Neurim Pharmaceuticals (1991) Ltd

27 Habarzel St
Tel Aviv 69710, ISRAEL

Phone: 972-3-7684902
Fax: 972-3-6494568
e-mail: talin@neurim.com

Sponsor Representative

Amnon Katz, PhD
VP, Clinical Development
Neurim Pharmaceuticals (1991) Ltd

27 Habarzel St
Tel Aviv 69710, ISRAEL

Phone: 972-3-7684906
Fax: 972-3-6494568
e-mail: amnonk@neurim.com

7. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATIONS

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)
ADCS-MCI-ADL	Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients
ADL	Activities of Daily Living
AE	adverse event
AHI	Apnea Hypopnea Index
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
CFT	Categorical Fluency Test
CGIC	Clinical Global Impression of Change
cNTB	computerized Neuropsychological Test Battery
COWAT	Controlled Oral Word Association Test
CPAP	continuous positive airway pressure
CSF	cerebrospinal fluid
CSSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICH E3	International Conference on Harmonisation Tripartite Guideline E3: Structure and Content of Clinical Study Reports
ICH E6	International Conference on Harmonisation Tripartite Guideline E6(R1): Good Clinical Practice
ISLT	International Shopping List Test
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
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI	Neuropsychiatric Inventory
NREM	non-rapid eye movement
NTB	Neuropsychological Test Battery
OBK	One Back Card
OCL	One Card Learning
PET	positron emission tomography
PK	pharmacokinetic(s)
PSA	prostate-specific antigen
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
SAE	serious adverse event
Sheehan-STS	Sheehan Suicidality Tracking Scale
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 postbaseline 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. People progressing to AD develop distressing changes in memory, thought, function, and behavior, which worsen over time. These changes increasingly impact the person's daily life and reduce their independence until ultimately these patients are entirely dependent on others (Querfurth and LaFerla, 2010). Worldwide, it is estimated that about 36 million people have dementia. Alzheimer's disease accounts for 50% to 80% of these patients (Duthey, 2013). At early-stage AD, the episodic memory is the most noticeable impairment (Gold and Budson, 2008). With the shift towards an increasingly elderly population, it is predicted that the number of people affected by early-stage AD that will progress to dementia will almost double every 20 years, and by the year 2050, 115 million people will have the condition (Duthey, 2013). 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 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 hallmark pathological feature of AD is the presence of brain plaques, consisting primarily of β-amyloid peptide (Aβ) aggregates (Selkoe, 2002). Accordingly, the abnormal production and aggregation of Aβ, associated particularly with late-stage disease, has been the principal target of many drug development efforts. However, 3 trials of Aβ lowering agents involving patients with overt dementia failed to show improvements in cognition. A leading theory posits that the attempts at intervention may have been made too late in the progression of disease, at a stage when neuronal damage had become too widespread, and therefore more trials now focus on patients in whom overt dementia seems imminent. An ideal drug for such patients will improve neuropsychological performance and functional abilities, slow down Aβ buildup, and promote neuroprotection and neurogenesis.

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. Through this unique molecular mode of action, piromelatine demonstrated in preclinical studies in rodents neuroprotective (Buendia et al., 2014, Tang et al., 2012), memory enhancing (He et al., 2013, Tian et al., 2010), sleep promoting (Liu et al., 2014), and neurogeneration enhancing capabilities (Tian et al., 2015 unpublished) with relevance to AD risk factors, comorbidities, and symptoms. The 5HT-1a agonists have demonstrated neuroprotective effects (Kline et al., 2004) by increasing both cell proliferation and neurogenesis in the hippocampal subgranular zone of the dentate gyrus and the subventricular zone (Banasr et al., 2004, Islam et al., 2014) and increase slow wave sleep (SWS) specifically by inhibition of hypothalamic orexin neurons and the dorsal raphe nuclei that act as wake promoting centers

(Muraki et al., 2004, Tabuchi et al., 2013). Simultaneous activation of melatonergic and 5HT-1a receptors may synergistically promote neurogenesis (Fava et al., 2012).

The sleep enhancing capacities of piromelatine may also be relevant to the therapeutic potential. Recent clinical and biochemical evidence has identified an interesting link between sleep, Aβ, cognitive dysfunction, and AD. In mice, Aβ clearance through the glymphatic system (the biomolecule clearance system operating the convective flow between the cerebrospinal fluid [CSF] and interstitial fluid to remove toxic metabolites) is strongly stimulated by sleep (Mendelsohn and Larrick, 2013, Xie et al., 2013). Bidirectional relationships between sleep and Aβ production have been demonstrated in mice overexpressing Aβ (Roh et al., 2012). In humans, normal soluble Aβ concentrations in the CSF fluctuate with the sleep-wake cycle with 6 hours delay (Huang et al., 2012). Disruption of non-rapid eye movement (NREM) SWS resulted in impaired overnight consolidation of long-term memory in healthy older adults (Mander et al., 2015). Since Aβ production is highest at times of neural activity such as during wakefulness and lowest at times of decreased neural activity such as during SWS, sleep disturbances accompanied by loss of SWS may lead to an increase in production of soluble CSF Aβ, increased Aβ aggregation, and attenuation of the Aβ diurnal pattern characterizing AD (Lucey and Bateman, 2014). Bidirectional relations between Aβ pathology and NREM sleep physiology were observed also in patients with mild cognitive impairment (MCI) and AD. In MCI patients the reduction in SWS was associated with deficits in sleep dependent memory consolidation (Pace-Schott and Spencer, 2015). Moreover, MCI patients had modified sleep structure characterized by shorter and disrupted SWS and lower Δ and Θ power as compared to controls (Westerberg et al., 2012). In AD patients, higher SWS was positively associated with retrieval of recent autobiographical memories (Rauchs et al., 2013).

Indeed, 63% of the patients with subtle cognitive deficits (also termed MCIs) (McKinnon et al., 2014) and 44% of the patients diagnosed with AD (Vitiello and Borson, 2001) demonstrate sleep disturbances as determined using the Pittsburgh Sleep Quality Index (PSQI). More recently, neuropathological analyses revealed a positive correlation between total sleep time, sleep quality, and sleep onset latency in demented and nondemented older adults with higher Aβ burden in specific brain areas that are linked to early AD (Spira et al., 2013). Accordingly, deterioration in cognition from healthy controls through MCI to AD patients was associated with parallel deterioration in sleep (Economou et al., 2013). The presence of insomnia may thus help identify patients with early signs of AD who are at a greater risk of deteriorating to dementia.

The relation becomes evident as poor sleep is directly associated with cognitive decline in healthy (Miyata et al., 2013) cognitively impaired (McKinnon et al., 2014), and demented adult populations (Vitiello et al., 1990), including AD (Carpenter et al., 1996, McCurry et al., 1999). Further exploration of interventions that promote NREM SWS and minimize the progression of neurodegeneration and the cognitive dysfunction associated with Aβ pathology is needed (Mander et al., 2015).

Importantly, the mechanism of sleep induction appears to be of key importance for the sought cognitive effects. Long-term use of benzodiazepine is associated with an increased risk of dementia (Billioti de Gage et al., 2012) and AD (Billioti de Gage et al., 2014, Yaffe and Boustani, 2014), presumably because of the known suppression of NREM SWS by benzodiazepines and nonbenzodiazepine hypnotics (Arbon et al., 2015). Treatment of patients with AD suffering from sleep disturbances with traditional hypnotics is associated with increased risk for a wide range of injuries (Chung et al., 2013, Diem et al., 2014) and may actually worsen

their cognition and memory (Hall-Porter et al., 2014). In contrast, melatonin receptor agonism, which maintains the NREM SWS (Arbon et al., 2015), appears beneficial for cognition and functioning in mild to moderate AD patients (Wade et al., 2014).

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 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 suggested dose-dependent beneficial effects of piromelatine on sleep continuity measures. 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 et al., 2012). In a Phase 2, randomized, placebo-controlled, sleep laboratory study in insomnia patients (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). 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 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 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.

Altogether, through its action at melatonin receptors, piromelatine may improve sleep, circadian rhythms control, and, subsequently, cognition in the patients (Wade et al., 2014). Through the serotonergic mechanism, piromelatine may improve memory and mood (Rodríguez et al., 2012), enhance SWS, and reduce wakefulness (Bjorvatn and Ursin, 1998, Monti and Monti, 2000). Through the combined activation of melatonergic and 5HT-1a receptors, piromelatine may act synergistically to increase neurogenesis (Fava et al., 2012).

This study is a Phase 2, randomized, placebo-controlled, dose-ranging study of piromelatine (5, 20, and 50 mg daily for 6 months) versus placebo to determine an effective dose to take forward to Phase 3 studies based on efficacy (cognitive performance), safety, and tolerability in patients with mild dementia due to AD.

9. OBJECTIVES OF THE STUDY

9.1 PRIMARY OBJECTIVE

The primary objective of the study is to compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the change from baseline in global composite score of the computerized Neuropsychological Test Battery (cNTB) after 26 weeks of double-blind treatment.

The global composite score includes the International Shopping List Test (ISLT; immediate and delayed recall), One Card Learning (OCL), Identification, Detection, and One Back Card (OBK).

9.2 SECONDARY OBJECTIVES

9.2.1 Key Secondary Objectives

1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on global impression assessed by the Clinical Global Impression of Change (CGIC) after 26 weeks of double-blind treatment
2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients (ADCS-MCI-ADL) at Weeks 13 and 26 and over 26 weeks of double-blind treatment

9.2.2 Other Secondary Objectives

1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog14) at Weeks 13 and 26 and over 26 weeks of double-blind treatment
2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the change from baseline in global composite score of the cNTB at Weeks 4 and 13 and over 26 weeks of double-blind treatment
3. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the episodic memory domain* composite score of the cNTB at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment

   * episodic domain tests: ISLT (immediate and delayed recall) and OCL
4. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the attention domain* composite score of the cNTB at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment

   * attention domain tests: Identification and Detection
5. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the executive function* composite score of the Neuropsychological Test Battery (NTB) at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment

   * executive function domain tests: OBK, Controlled Oral Word Association Test (COWAT) and Categorical Fluency Test (CFT)
6. To compare the safety and tolerability of piromelatine (5, 20, and 50 mg) to that of placebo

9.2.3 Exploratory Objectives

1. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on cognitive aspects of mental function assessed by the Mini-Mental State Examination (MMSE) after 2 weeks of run-in single-blind placebo followed by 26 weeks of double-blind treatment

2. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in individual cNTB test scores (ISLT immediate and delayed recall, OCL, Identification, Detection, OBK) at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment
3. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on the change from baseline in behavioral signs and symptoms assessed by the Neuropsychiatric Inventory (NPI) scale after 26 weeks of double-blind treatment
4. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo on sleep variables derived from the PSQI at Weeks 4, 13, and 26 and over 26 weeks of double-blind treatment
5. To compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in ADAS-cog13, ADAS-cog12, and ADAS-cog11 score at Weeks 13 and 26, and over 26 weeks of double-blind treatment.

10. INVESTIGATIONAL PLAN

10.1 OVERALL STUDY DESIGN AND PLAN

This is a Phase 2, double-blind, parallel-group, placebo-controlled, dose ranging safety and efficacy study of piromelatine in patients with mild dementia due to AD.

Following informed consent, patients with a documented history of mild dementia due to AD for at least 6 months, having an MMSE score of 20 to 27 (inclusive) at Screening (a score of 27 is allowed only if accompanied by a score of ≥ 12 in the ADAS-cog11 portion of the ADAS-cog14 at Screening) and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1 will be recruited and further screened for eligibility. Caregiver 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). A computed tomography (CT) or magnetic resonance imaging (MRI) scan will be obtained to rule out clinically significant comorbid pathologies for patients who did not have this scan in the last 12 months before Screening. Patients who had a past (more than 12 months or less than 12 months before) CT or MRI scan indicating incompatibility with a diagnosis of probable AD should not be screened. The medical monitor should be contacted when there are questions about eligibility. 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, and documented history of cognitive deterioration of these potential eligible patients to be centrally reviewed. After confirmation of eligibility from the central reviewer, 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 1.2:1:1:1 randomization ratio to the 4 trial arms (placebo [1.2], and the equal piromelatine treatment arms 5, 20, and 50 mg [1:1:1]).

Intermediate visits will be carried out at 4 weeks (Visit 3) and 13 weeks (Visit 4) 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 5 (Week 26) will be brought back for a termination visit.

Piromelatine 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

		Single-Blind Run-in		Double-Blind Treatment			
Period	**Screening**	**Run-in**	**Randomization**				**Follow-up Phone call**
Week		–2	0	4	13	26	28
Visit	1		2	3	4	5	
Treatment		Placebo		Piromelatine 5, 20, or 50 mg or Placebo			N/A

The Schedule of Assessments is presented in Table 10.1.

Table 10.1: Schedule of Assessments

Period	**Single-Blind Run-in**		**Double-Blind Treatment**			**Follow-up** [a]	**Premature Discontinuation Visit**
Visit	**1** [b]	**2**	**3**	**4**	**5**		
Study Day	**–25 to 14**	**0 ± 3***	**28 ± 3**	**91 ± 5**	**182 ± 5**	**196**	
Study Week		**0**	**4**	**13**	**26**	**28**	
Explanation of the study	X						
Informed consent - patient	X						
Informed consent - caregiver	X						
Screening number assigned	X						
Demographic data	X						
MMSE	X				X		
CDR	X						
Medical and surgical history	X						
CT/MRI [c]	X						
PET/CSF data collection [d]	X						
Inclusion and exclusion criteria	X	X					
Randomization		X					
Physical examination	X			X	X		X
Vital signs	X	X	X	X	X		X
BMI	X				X [e]		
Concomitant medications	X	X	X	X	X		X
12-lead ECG	X			X	X		X
Hematology/biochemistry/ urinalysis	X			X	X		X
Hormonal testing [f]	X				X		X
Blood sampling for ApoE4 genotyping [g]					X		
Urine drug screen (BZDs and opiates)	X			X [h]			
Recording of adverse events		X	X	X	X	X	X
Sheehan-STS	X			X	X		X
Compliance verification		X	X	X	X		
Computerized NTB	X [i]	X [j]	X	X	X		
ADAS-cog14	X [i]	X		X	X		
CGIC		X		X	X		
ADCS-MCI-ADL		X		X	X		
Executive function (COWAT, CFT)	X [i]	X	X	X	X		
NPI		X			X		

Period	**Single-Blind Run-in**		**Double-Blind Treatment**			**Follow-up** [a]	**Premature Discontinuation Visit**
Visit	**1** [b]	**2**	**3**	**4**	**5**		
Study Day	**–25 to 14**	**0 ± 3***	**28 ± 3**	**91 ± 5**	**182 ± 5**	**196**	
Study Week		**0**	**4**	**13**	**26**	**28**	
PSQI		X	X	X	X		
MMSE, CDR, ADAS-cog, and documented history of cognitive deterioration for central review	X						
Study medication dispensed	X	X	X	X			
Collection of unused study medication and used packs since last visit		X	X	X	X		X
Run-in phone call [k]	X						
Compliance phone call (every week between Visits 2-5) [l]	On Days (±3) 7, 14, 21, 35, 42, 49, 56, 63, 70, 77, and 84 On Days (±5) 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168, and 175						

Key: ADAS-cog14 = Alzheimer's Disease Assessment Scale (cognitive subscale); ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients; ApoE4 = apolipoprotein-E (gene); BMI = body mass index; BZD = benzodiazepine; CDR = Clinical Dementia Rating; CFT = Categorical Fluency Test; CGIC = Clinical Global Impression of Change; COWAT = Controlled Oral Word Association Test; CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; NTB = Neuropsychological Test Battery; PET = positron emission tomography; PSQI = Pittsburgh Sleep Quality Index; Sheehan-STS = Sheehan Suicidality Tracking Scale.

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

[b] 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.

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

[d] Blood samples should be drawn in the morning. If the blood sample at Visit 1 is drawn in the afternoon, then the Visit 5 sample should also be drawn in the afternoon.

[e] Retrospective genetic information could be used.

[f] To be repeated randomly in some patients during the study.

[g] Practice session.

[h] There are 2 administrations of the computerized NTB at Visit 2, performed 15 minutes apart.

[i] On Day –14, after eligibility by central reviewer.

[j] The caregiver 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).

[k] Only weight.

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

10.2 DISCUSSION OF STUDY DESIGN

Piromelatine proposed mode of action and previous studies suggest that this molecule may improve cognitive performance via its effects on sleep and neuroprotective pathways. Sleep effects were demonstrated after 4 weeks of treatment in a Phase 2 sleep laboratory study. Cognition effects are expected to be seen after 26 weeks of treatment as has been shown previously with melatonin administered to a similar population of patients (Wade et al., 2014).

The cognitive outcome measure mostly used in AD clinical trials, the ADAS-cog, 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 et al., 2013). However, over the past 10 years the ADAS-cog has been shown to have poor sensitivity in discerning cognitive change in patients with MCI and early AD (Gold, 2007; Greenberg et al., 2013; Grundman et al., 2004; Sevigny et al., 2010). Given the importance of formal neuropsychological approaches to the diagnosis and management of AD in patients with mild and moderate AD, several neuropsychological tests have been combined to construct a Neuropsychological Test Battery (NTB) (Harrison et al., 2007). In accord with the approaches to constructing the NTB for clinical trials in AD, the tests to be used in the NTB for this study have been selected on the basis of the following:

a) demonstrated validity for the target cognitive domain

b) demonstrated acceptability in patients with some diminished intellectual function due to AD

c) acceptable estimates of test-retest reliability in patients with AD

d) demonstrated sensitivity to cognitive change in AD (eg, related to drug effects or disease progression)

Dosage specification was made on the basis of previous studies and the relative affinity to the melatonin and serotonin receptors.

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

The use of placebo allows for a blinded, thus minimally biased, study. The placebo group is a comparator group for efficacy and safety assessment.

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 assessment prior to their baseline measurements (NTB and ADAS-cog14).

10.3. SAFETY MONITORING AND DATA AND SAFETY MONITORING BOARD

Safety data will be reviewed on an ongoing basis by the sponsor (Neurim Pharmaceuticals [1991] Ltd) and the medical monitor. Safety data will also be reviewed on an ongoing basis by an independent Data and Safety Monitoring Board (DSMB). The DSMB will be assembled to review safety and tolerability data collected during the study. Based on its ongoing assessment of

the safety and tolerability of piromelatine, the DSMB will provide recommendations to the sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and in the Statistical Analysis Plan.

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 the 2-week single-blind, placebo run-in period, eligible patients at Visit 2 will be randomized and treated with piromelatine (5, 20, or 50 mg) or placebo as a double-blind treatment for 26 weeks. Assuming a 50% screen failure rate and allowing for 15% patient withdrawal, 1150 patients should be screened in order to randomly assign 575 patients, of whom it is expected 500 will complete the study.

11.1.2 Inclusion Criteria

1. Patient has a permanent caregiver (participant's caregiver is not expected to change during the course of the study) who will, accompany the patient to the office and/or be available by telephone at designated times, monitor administration of prescribed medications, control the minimum 2-hour daily light exposure requirement, and be responsible for the overall care of the patient at home. Caregiver must, in the opinion of the investigator, have enough contact with the participant to be able to perform the duties described above.
2. Patient and caregiver are willing to take part in the entire study.
3. Signed informed consent from the patient who is capable to sign the consent form as judged by the study investigator and from the caregiver as dictated by local legal circumstances.
4. Patient is a male or female aged 60-85 years (inclusive).
5. Patient is an outpatient living at home or in an assisted living facility with no plans to move or travel during the investigational period.
6. Patient has a clearly documented history either in medical records or from an informant of cognitive decline over at least 6 months. If available, any scale verification of the decline should be requested.
7. Patient has mild probable AD as consistent with criteria established by the NIA-AA (McKhann et al., 2011).
8. Patient has MRI or CT scan, performed within 12 months before Screening, with findings consistent with the diagnosis of dementia due to AD without any other clinically significant comorbid pathologies. If this MRI or CT scan is unavailable, or occurred more than 12 months before Screening this assessment should be completed and the findings confirmed prior to Visit 2 (copy of the report will be available at the study site).
9. Patient has an MMSE score of 20-27 (inclusive) at Screening (a score of 27 is allowed only if accompanied by a score of ≥ 12 in the ADAS-cog11 portion of the ADAS-cog14

at Screening; patients with an MMSE score of 19 may be rescreened once after 1 month).

10. Patient has a CDR-GS of 0.5-1 (mild dementia) at Screening.
11. Patients taking acetylcholinesterase inhibitors 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 must be agreeable to not starting throughout the study.
13. Patients who stopped receiving acetylcholinesterase inhibitors must be stable off acetylcholinesterase inhibitors for 6 months before Visit 2 (Baseline) and must be agreeable to not restarting throughout the study.
14. Patient has a negative drug screen (benzodiazepines or opiates) at Screening.
15. Female patients must have had last natural menstruation ≥ 24 months before Screening, OR be surgically sterile.
16. 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.
17. Patients who are taking medications for nonexcluded concurrent medical conditions should be on a stable dose for at least 4 weeks before Screening. Patients taking allowed antidepressants or memantine (see Section 12.9) should be on a stable dose for at least 3 months before Screening and throughout the study.
18. Patients who are taking vitamin B12 should be on a stable dose for at least 3 months before Screening and throughout the study.
19. Patient is able to ingest oral medication and participate in all scheduled evaluations.
20. 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).
21. Patient and caregiver have the ability to read and write in English (or Spanish if using Spanish materials) and have hearing, vision, and physical abilities adequate to perform assessments (corrective aids allowed).

11.1.3 Exclusion Criteria

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

1. Patient has an alternative cause for dementia other than AD.
2. A past or recent CT or MRI scan or report indicating brain pathology that is associated with cognitive impairment or incompatible with a diagnosis of probable AD (e.g., any cortical infarct defined as > 1.5 cm3; more than 2 lacunar infracts defined as ≤ 1.5 cm^3;

diffuse white matter disease). The medical monitor should be contacted when there are questions about eligibility.

3. Patient has evidence of any clinically significant neurodegenerative disease, or other serious neurological disorders other than AD, including but not limited to:
    a) Frontotemporal dementia, dementia with Lewy bodies, or vascular dementia documented by clinical history
    b) History or presence of any stroke with clinical symptoms ≤ 2 years before Screening
    c) Epilepsy or history of seizures, except for simple childhood febrile seizures or alcohol withdrawal seizures
    d) History of clinically relevant head trauma with neurological sequelae
    e) Parkinson's disease
    f) Multiple sclerosis
    g) Amyotrophic lateral sclerosis
    h) Myasthenia gravis
    i) Moderate to severe sleep apnea (Apnea Hypopnea Index [AHI] $\geq$ 15); use of continuous positive airway pressure (CPAP) or other sleep-related devices for sleep apnea
    j) Narcolepsy
4. Patient has been diagnosed with the following Axis I disorders (Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-V] criteria):
    a) Schizophrenia spectrum and other psychotic disorders (not related to dementia)
    b) Bipolar and related disorders
    c) Substance use disorders within the past 2 years
5. Patient has a history of uncontrolled or untreated cardiovascular, endocrine, gastrointestinal, respiratory, or rheumatologic disorders within the past 5 years.
6. Patient has a history of severe agitation.
7. Patient has a known history of human immunodeficiency virus (HIV).
8. Patient has a history of serious infectious disease including:
    a) Neurosyphilis
    b) Meningitis
    c) Encephalitis
9. 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).

10. Patient has severe pain that is likely to interfere with sleep (in the opinion of the investigator).
11. 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 µ3 if due to chronic alcoholism
    d) Renal failure with creatinine > 150 µmol/L
12. Patient is unable to adequately perform the computerized testing as judged by the study investigator or investigator designee at the practice session during Screening.
13. Continuous use of benzodiazepines or other sedative-hypnotics during the 2 weeks before Screening (see Section 12.9).
14. Patient has a history of chronic use and abuse of benzodiazepines or other sedative-hypnotics.
15. Use of any kind of melatonin/melatonin agonist during the 2 weeks before Screening (see Section 12.9).
16. Patient has known or suspected hypersensitivity to exogenous melatonin or melatonin receptor agonists.
17. Patient has clinically significant abnormal laboratory findings that have not been approved by the study safety officer.
18. Patient has persistent bradycardia (heart beat < 50 bpm) or tachycardia (heart beat > 100 bpm).
19. 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).
20. Patient has other serious diseases that could interfere with patient assessment, in the opinion of the investigator.
21. Patient has untreated B12 and/or folic acid deficiency.
22. 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.
23. Patient with a body mass index (BMI) above 35 or below 18.

24. 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)
25. Administrative exclusion
    a) Patient and/or caregiver unable to contact the investigator by phone in case of an emergency
26. Patients with evidence of serious risk of suicide based on the Sheehan Suicidality Tracking Scale (Sheehan-STS); ie, a score of 3 or 4 question 2 or 13 and a score of 2 or higher on questions 1a, 3 through 12 and 14, 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.

For patients found eligible by the sites, records of the MMSE, CDR, and documentation of cognitive decline complaint over at least 6 months by patient will be reviewed. The results of the ADAS-cog14 administered as a practice session during Screening will be reviewed as well. The ADAS-cog11 portion of the ADAS-cog14 will be part of the eligibility approval only in cases where the MMSE score is 27. MMSE, CDR, and ADAS review will also include audio capture and review of the interviews.

These records will be reviewed by a team of independent certified clinicians who will approve eligibility. In cases where issues are identified, the investigator will be contacted to discuss patient eligibility on a peer-to-peer basis. The discussion will include the relevant data, the possible exclusionary finding, and any new data the investigator may have gathered. A decision to enroll a patient will be made by the investigator after consultation with the reviewing clinician. All communication regarding subject eligibility will be documented and filed.

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 2-week, single-blind, run-in period and a 26-week, randomized, double-blind treatment period, for a total of 28 weeks. Two weeks after last dosing of study medication, the caregiver 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 randomized treatment.

An integrated clinical study report in the format of the International Conference on Harmonisation 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 in a 1.2:1:1:1 ratio to placebo (1.2) or to 1 of 3 active treatment arms (1:1:1) as follows:

Active Medication

Piromelatine 5, 20, or 50 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 tablets are pink and oval shaped. Tablets will be packaged in polyethylene terephthalate bottles containing 35 tablets. 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 3 days after the scheduled date. For the period between Visit 2 (randomization) and Visit 3 (Week 4), each patient will receive 1 bottle with 35 tablets. For the period between Visit 3 (Week 4) and Visit 4 (Week 13), each patient will receive 2 bottles containing 35 tablets each (total of 70 tablets). For the period between Visit 4 (Week 13) and Visit 5 (Week 26), each patient will receive 3 bottles containing 35 tablets each (total of 105 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, bottle 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 doses (5, 20, and 50 mg) 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 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 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). 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 et al., 1998). Both effects may be beneficial for AD patients to enhance Aβ clearance from the brain.

12.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Commencing at Visit 1, all patients will be assigned an identification number. This identification number and the patient's 3 initials 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 4 trial arms.

12.5 SELECTION AND TIMING OF DOSE FOR EACH PATIENT

Upon completion of eligibility review, the caregiver will be instructed via telephone call to begin administration of study medication. 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 (5, 20, or 50 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.

12.6 DOSE ADJUSTMENT CRITERIA

The dose will not change throughout the 26-week randomized double-blind treatment period.

12.7 BLINDING

The initial 2-week run-in period of this study 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, where the investigators, staff, and patients will be unaware of the 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

Genetic testing for apolipoprotein E (APOE4) status is voluntary. Retrospective genetic information could be used. Patients requiring a blood test for APOE4 status must sign a separate ICF. The test should be performed during the patient’s last visit.

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 6 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 3 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

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

Patients taking alternative pharmacotherapy for dementia (eg, 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 (eg, 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 ($\leq$ 6.25 mg controlled release and $\leq$ 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.

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 –25 to -14)

- Explanation of the study
- Patient and caregiver 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 caregiver
    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 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
- Urine drug screen for benzodiazepines and opiates
- Recording of concomitant medication(s)
- Sheehan-STS
- Practice session with cNTB
- Practice session with ADAS-cog14 (score of ≥ 12 in the ADAS-cog11 portion of the scale is required and should recorded if MMSE score is 27)
- Practice session with executive function measurements (COWAT, CFT)

- Uploading MMSE, CDR, ADAS-cog, and documented history of cognitive deterioration for central review
- Dispensing of study medication (placebo) – caregiver will be instructed via telephone call to open the bottle and start the run-in period upon confirmation of eligibility. 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 caregiver must be present both days, and the following screening procedures should be completed on the indicated day:

- Screening Day 1: MMSE, ADAS-cog, cNTB
- Screening Day 2: COWAT/CFT, CDR, Sheehan-STS

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 caregiver 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 ± 3 days [from the end of run-in])

- 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 13.3.2)
- 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
- cNTB (ISLT immediate and delayed recall, OCL, identification, detection, OBK) completed by the patient **WITH** the investigator or investigator designee
- CGIC completed by an investigator designee (should not be completed by the principal investigator) with the patient and caregiver; the CGIC assessor must be blinded to all other data for the patient after Visit 2
- ADCS-MCI-ADL completed by the investigator or investigator designee with the caregiver
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- Executive function measurements (COWAT, CFT) completed by the investigator or investigator designee with the patient

- NPI completed by the investigator or investigator designee with the caregiver
- Patient PSQI completed by the investigator or investigator designee with the patient and caregiver
- 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, and 21 ± 3, the caregiver 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 4 (Day 28 ± 3 days)

- Vital signs measurements
- Recording of concomitant medication(s)
- Recording of AEs
- Compliance verification
- cNTB (ISLT immediate and delayed recall, OCL, identification, detection, OBK) completed by the patient **WITH** the investigator or investigator designee
- Executive function measurements (COWAT, CFT) completed by the investigator or investigator designee with the patient
- Patient PSQI completed by the investigator or investigator designee with the patient and caregiver
- 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 35 ± 3, 42 ± 3, 49 ± 3, 56 ± 3, 63 ± 3, 70 ± 3, 77 ± 3, and 84 ± 3, the caregiver 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 13 (Day 91 ± 5 days)

- Physical examination and vital signs measurements, including 12-lead ECG
- Recording of concomitant medication(s)
- Recording of AEs (see Section 13.3.2)
- 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)
- Sheehan-STS
- Compliance verification
- cNTB (ISLT immediate and delayed recall, OCL, identification, detection, OBK) completed by the patient **WITH** the investigator or investigator designee
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- CGIC completed by an investigator designee (should not be completed by the principal investigator) with the patient and caregiver; the CGIC assessor must be blinded to all other data for the patient after Visit 2
- ADCS-MCI-ADL completed by the investigator or investigator designee with the caregiver
- Executive function measurements (COWAT, CFT) completed by the investigator or investigator designee with the patient
- Patient PSQI completed by the investigator or investigator designee with the patient and caregiver
- 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 98 ± 5, 105 ± 5, 112 ± 5, 119 ± 5, 126 ± 5, 133 ± 5, 140 ± 5, 147 ± 5, 154 ± 5, 161 ± 5, 168 ± 5, and 175 ± 5 the caregiver 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 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 13.3.2)
- Collection of blood and urine samples for urinalysis, hematology, biochemistry, and hormonal tests
- Collection of blood samples for ApoE4 genotyping (for those patients who agree to sign separate ICF for genetic testing)
- Body weight measurement
- Sheehan-STS
- Compliance verification

- cNTB (ISLT immediate and delayed recall, OCL, identification, detection, OBK) completed by the patient **WITH** the investigator or investigator designee
- MMSE completed by the investigator or investigator designee with the patient
- CGIC completed by investigator designee (should not be completed by the principal investigator) with the patient and caregiver; the CGIC assessor must be blinded to all other data for the patient after Visit 2
- ADCS-MCI-ADL completed by the investigator or investigator designee with the caregiver
- ADAS-cog14 completed by the investigator or investigator designee with the patient
- Executive function measurements (COWAT, CFT) completed by the investigator or investigator designee with the patient
- NPI completed by the investigator or investigator designee with the caregiver
- Patient PSQI completed by the investigator or investigator designee with the patient and caregiver
- 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, ADAS-cog, cNTB, COWAT/CFT, CDR, Sheehan-STS

Visit 2: cNTB (×2), ADAS-cog, COWAT/CFT, CGIC, PSQI

Visit 3: cNTB, COWAT/CFT, PSQI

Visit 4: cNTB, ADAS-cog, COWAT/CFT, CGIC, PSQI, Sheehan-STS

Visit 5: cNTB, ADAS-cog, COWAT/CFT, CGIC, MMSE, PSQI, Sheehan-STS

Caregiver:

Visit 1: CDR

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

Visit 3: PSQI (with patient)

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

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

IMPORTANT NOTE: The investigator or investigator designee must be present throughout the entire session to assist the patient in completing all of the computerized NTB subtests (ISLT immediate and delayed recall, OCL, identification, detection, OBK).

Investigator or investigator designee will have to confirm by signing that he/she was present throughout the entire session.

***Please note that only raters with a "Qualified" status (in the Site Status Memo that each site receive occasionally from Bracket) 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 caregiver to elicit any safety concerns for the purpose of recording AEs.

Premature Discontinuation Visit

The investigator 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
- Sheehan-STS

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

13.1 CLINICAL EFFICACY PARAMETERS

13.1.1 Primary Efficacy Parameter

The primary efficacy parameter is the cNTB (global composite of 5 test scores):

1. Visual recognition learning task (OCL): The OCL task is a continuous visual recognition learning task that assesses visual learning within a pattern separation model. Theoretical models of the pattern separation model specify that information is organized in orthogonal and distinct nonoverlapping representations so that new memories can be stored rapidly without interference. The OCL has been shown to be a valid test of learning and memory in MCI and AD. In this task, the patient must attend to the card in

the center of the screen and respond to the question, "Have you seen this card before in this task?" If the answer is yes, patients are instructed to press the "YES" button, and the "NO" button if the answer is no. Normal playing cards are displayed (without joker cards). In this task, 4 cards are drawn at random from the deck and are repeated throughout the task. These 4 cards are interspersed with distractors (nonrepeating cards). The task ends after 80 trials, without rescheduling for postanticipatory correct trials. The primary performance measure for this task is the proportion of correct answers (accuracy), which is normalized using an arcsine square root transformation.

2. Verbal Learning Task (ISLT – immediate and delayed): The ISLT is a computer-controlled verbal learning test. In this test, patients are read a list of 12 words. Each word is a concrete noun and describes an item of food that is found commonly in the culture/society in which testing is occurring. The examiner asks the patient "I am going to read to you a list of items I want you to get from the supermarket/store/market/shop etc." After the 12 words have been read, the patient is asked to recall as many of the words as he/she can. If he/she can recall no more words, the same list is read a second time with the words in the same order after the same instruction. The process of reading the list and waiting for responses occurs 3 times. At the completion of the computerized battery, the patient is asked to recall as many of the items as he/she can from the shopping list. This provides a measure of delayed recall. The primary performance measure for this task is the total number of correct words recalled.
3. Detection task: The Cogstate Detection task is a measure of simple reaction time and has been shown to provide a valid assessment of psychomotor function in healthy adults and in adults with MCI and AD. For this test, the patient must press a "YES" response key as soon as he/she detects an event (ie, a card turning face up presented in the center of the computer screen). The software measures the response time to detect each event.
4. Identification task: The Cogstate Identification task is a measure of choice reaction time and has been shown to provide a valid assessment of visual attention in MCI and AD. In this task an event (a card turning face up) occurs in the center of the computer screen and the patient must decide "YES" or "NO" as to whether this event meets a predefined and unchanging criterion (eg, is the color of the card red?). The software measures the speed and accuracy of each response.
5. Computerized One Back Working Memory task (OBK): The Cogstate One Back memory task is a valid measure of working memory in MCI and AD. On this task the patient is shown a single stimulus in the center of the computer screen (a card turns face up). The patient must decide "YES" or "NO" as to whether the current card matches the card that had been seen on the immediately previous trial. The software measures the speed and accuracy of each response.

13.1.2 Secondary Efficacy Parameters

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 caregiver 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 et al., 1997; Schneider et al., 2006). The ADCS-CGIC assessor must be blinded to all other data for the patient after Visit 2.

Daily living activity (ADCS-MCI-ADL)

The ADCS-MCI-ADL 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 et al., 2006). The ADCS-MCI-ADL is an 18-item interview–based assessment (questions 19-24 are not to be completed), and its ratings will be based on an interview of the patient's best (closest) informant by a rater from the clinic. Scale administration duration will be about 15-30 minutes.

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 et al., 2011).

Global Composite Score of the cNTB (composite of 5 test scores)

The global composite score of the cNTB is a composite score of the ISLT (immediate and delayed recall), OCL, Identification, Detection, and OBK tests. For more details on the individual tests, please refer to Section 13.1.1.

Episodic Memory Domain of the cNTB (composite of 2 test scores)

The episodic memory domain of the cNTB is a composite score of the ISLT (immediate and delayed recall) and OCL tests.

Attention Domain of the cNTB (composite of 2 test scores)

The attention domain of the cNTB is a composite score of the Identification and Detection tests.

Executive Function Domain (composite of 3 test scores)

1. Computerized One Back Working Memory task (OBK)
2. Category Fluency Test (CFT): In this task, the patient is given a category and is instructed to provide as many items as he/she can that belong to this category in 60 seconds. The score on this test is the total number of correct words provided for each category.

3. Controlled Oral Words Association Test (COWAT): The COWAT is a cognitive test of verbal processing ability used to assess brain impairment. Verbal processing ability and verbal fluency are considered executive functions. The emphasis on these tests focuses on the degree of discrepancy (as opposed to consistency) between current functioning and an estimated pre-impairment functioning. The COWAT assesses the patient's ability to spontaneously produce words that begin with specific letters within a certain time limit. In particular, the test uses the letters F, A, and S.

13.1.3 Exploratory Efficacy Parameters

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.

cNTB – Individual Scores

The individual scores of the cNTB include ISLT (immediate and delayed recall), OCL, Identification, Detection, and OBK.

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 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 caregiver rate each of these 7 areas of sleep. In cases of discrepancies, the caregiver 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 et al., 1989).

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 et al., 2011).

Sheehan Suicidality Tracking Scale

The Sheehan-STS is a prospective rating scale that tracks both treatment-emergent suicidal ideation and behaviors. The Sheehan-STS is a 22-item scale that can be administered by either a clinician or patient through self-report.

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 (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 13), and Visit 5 (Week 26; end-of-study visit). The Sheehan-STS will also be rated at Visit 1 (Screening), Visit 4 (Week 13), and Visit 5 (Week 26; end-of-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), 4, and 5 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.

Prolactin and testosterone levels will be measured from blood samples collected at Visits 1 and 5.

13.3.2 Adverse Events

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

Eliciting and Documenting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. 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. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, which do not represent a clinically significant exacerbation or worsening, need not be considered AEs.

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

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

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.

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

Assessment of Frequency

Frequency should be assessed using the following categories:

- unique
- intermittent
- continued

Assessment of Outcome

Outcome should be assessed using the following categories:

- recovered
- recovered with sequelae

- not recovered
- unknown

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:

- not related
- unlikely to be related
- possibly related
- probably related
- definitely related

Follow-up of Adverse Events

All investigators should follow-up with patients on AEs until the event 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.

13.3.3 Suicidal Ideation

Suicidal ideation will be rated at Visit 1 (Screening), at Visit 4 (Week 13), and at Visit 5 (Week 26; end-of-study visit) using the Sheehan-STS. At Screening, patients with evidence of serious risk of suicide based on the Sheehan-STS with a score of 3 or 4 on question 2 or 13 and a score of 2 or higher on questions 1a, 3 through 12, and 14 should be excluded from the study. During the study (at Visit 4), patients should be discontinued from the study if they score 3 or 4 on any one question 2 through 8 or 13, or score 2 or higher on any one question 1a, 9 through 12, or 20, or if, in the opinion of the investigator, the patient present a serious risk of suicide.

14. SERIOUS ADVERSE EVENTS

14.1 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; ie, 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. In addition, medical and scientific judgment is required to decide if prompt notification is required in other situations; ie, 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 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

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

14.3 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 study medication, whether or not the SAE is related to the study medication. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. A copy of these forms must be faxed **within 24 hours** following knowledge of the event by the investigator for the attention of the medical monitor at:

Name: Enrique Comesaña, MD, MBA
Title: Executive Medical Director
Company: INC Research, LLC
Email: enrique.comesana@incresearch.com
Office: (737) 484-3304
Mobile: (512) 367-0592
Fax: (737) 209-7302

INC Research will inform Neurim Pharmaceuticals of any deaths, life-threatening SAEs, or drug-related SAEs within 1 working day and within 2 working days for all other SAEs. The sponsor's safety officer will inform the qualified person in pharmacovigilance of any suspected unexpected serious adverse reaction (SUSAR) within 24 hours of receipt. The safety officer will inform the qualified person in pharmacovigilance immediately of any developing safety concern.

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 immediately.

14.4 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: Enrique Comesaña, MD, MBA
Title: Executive Medical Director
Company: INC Research, LLC
Email: enrique.comesana@incresearch.com
Office: (737) 484-3304
Mobile: (512) 367-0592
Fax: (737) 209-7302

In addition, the sponsor's 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

14.5 REGULATORY RESPONSIBILITY

INC Research, 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 also 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

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.

INC Research 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 documented.

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 1.2:1:1:1 randomization ratio to the 4 trial arms (placebo [1.2] and the equal piromelatine treatment arms 5 mg, 20 mg, and 50 mg [1:1:1]). Assuming an effect size between treatment dose and placebo of 0.35 over 26 weeks, a significant level (α) of 0.05, and power of 88%, a sample size of 143 patients for the placebo arm and 119 for each of the 3 piromelatine arms is calculated. Assuming a 50% screen failure rate and allowing for 15% patient withdrawal, 1150 patients should be screened in order to randomly assign 575 patients, of whom it is expected 500 will complete the study.

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 one-tailed at the 5% level of significance. The justification for this follows. When conducting placebo-controlled trials, it is imperative that the study medication be demonstrated to be superior in efficacy to placebo, since equivalent or worse efficacy than placebo will preclude approvability. Consequently, a one-sided test for efficacy is required. The null hypothesis is that the drug is equal or worse than placebo. The alternative hypothesis is that the drug has greater efficacy than placebo. A Type I error occurs only when it is concluded that a study medication is effective when in fact it is not. This can occur in only one tail of the distribution of the treatment difference.

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, 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 cNTB global composite score (ISLT immediate and delayed recall, OCL, identification, detection, and OBK) will be summarized at baseline and after 4, 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 will be carried out using an analysis of covariance (ANCOVA) model with treatment and study site as the main effects and baseline cNTB global z-score as the covariate. To evaluate the effect of missing cNTB items, multiple imputations will be used for the calculation of cNTB composite scores in the case of 1 or 2 missing cNTB items.

Secondary efficacy analyses will be carried out using a mixed-effects maximum likelihood repeated measures (MMRM) model utilizing all baseline and postbaseline data to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, study site, visit, and treatment by visit interaction, with baseline score as a covariate, and a baseline by visit interaction. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values.

17.3.3 Analysis of Secondary Efficacy Parameters

The same aforementioned ANCOVA model will be used to analyze all secondary efficacy endpoints: CGIC, ADCS-MCI-ADL, ADAS-cog14, cNTB global composite score, cNTB episodic memory domain composite score (ISLT and OCL), cNTB attention domain composite score (identification and detection), and executive function composite score (OBK, COWAT and CFT). The MMRM model also will be used for the analysis of ADCS-MCI-ADL, cNTB various domains composite score (identification and detection) and executive function composite score.

17.3.4 Analysis of Exploratory Efficacy Parameters

The same aforementioned ANCOVA model will be used to analyze the exploratory efficacy endpoints: MMSE, individual cNTB scores, NPI, PSQI (global score and individual components), and ADAS-cog13, ADAS-cog12, and ADAS-cog11 scores.

Additionally, the MMRM model will be used for the analysis of individual cNTB scores and the PSQI global and individual component scores.

17.3.5 General Considerations

For all ANCOVA and MMRM models, data collected from investigators who enrolled fewer than 3 patients in any 1 treatment group will be combined prior to analysis. If this combination still results in a treatment group having fewer than 3 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, change in physical examination parameters, and vital signs. 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.

The number of patients reporting AEs will be summarized during the 28-week treatment period by body system 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 will be summarized using shift tables 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.

The change in physical examination parameters from baseline to the end of the 28-week treatment period 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 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 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, 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 Harmonisation (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 INC Research 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 INC Research 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 INC Research 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 INC Research 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 INC Research. 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 INC Research 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 INC Research.

Patients who are willing to participate in the ApoE4 genotyping will be asked to sign a separate applicable ICF.

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 (eg, medical records, appointment books, original laboratory records). These personnel will not disclose any of the patient's personal medical information.

Each caregiver 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 caregiver. Informed consent will be documented by the use of a written information sheet approved by the IRB and signed by the caregiver. The signature confirms the consent is based on information that has been understood. Each caregiver's signed information sheet must be kept on file by the investigator for possible inspection by regulatory authorities, Neurim Pharmaceuticals, or INC Research 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 (eg, 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, INC Research, 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
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
ANTICHOLINERGIC AGENTS	Anti-Muscarinic agents	Scopolamine	PROHIBITED

Drug Category	Drug Subcategory	Medication-PT	Status
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

Drug Category	Drug Subcategory	Medication-PT	Status
ANTIDEPRESSANTS	MAOI (Reversible)	Pirazidol	PROHIBITED
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)

Drug Category	Drug Subcategory	Medication-PT	Status
ANTIDEPRESSANTS	Tricyclic antidepressants	Doxepin	PROHIBITED (TAC with high sedative/ anticholinergic action)
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

Drug Category	Drug Subcategory	Medication-PT	Status
ATYPICAL ANTIPSYCHOTICS	Atypical	Lurasidone	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Lurasidone Hydrochloride	PROHIBITED
ATYPICAL ANTIPSYCHOTICS	Atypical	Zotepine	PROHIBITED
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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
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

Drug Category	Drug Subcategory	Medication-PT	Status
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. REFERENCES

ARBON, E. L., KNUROWSKA, M. & DIJK, D. J. 2015. Randomised clinical trial of the effects of prolonged-release melatonin, temazepam and zolpidem on slow-wave activity during sleep in healthy people. *J Psychopharmacol*. 29(7):764-76.

BANASR, M., HERY, M., PRINTEMPS, R. & DASZUTA, A. 2004. Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. *Neuropsychopharmacology.* 29(3):450-60.

BILLIOTI DE GAGE, S., BÉGAUD, B., BAZIN, F., VERDOUX, H., DARTIGUES, J.-F., PÉRÈS, K., KURTH, T. & PARIENTE, A. 2012. Benzodiazepine use and risk of dementia: prospective population based study. *BMJ.* 345:1-12.

BILLIOTI DE GAGE, S., MORIDE, Y., DUCRUET, T., KURTH, T., VERDOUX, H., TOURNIER, M., PARIENTE, A. & BÉGAUD, B. 2014. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ.* 349:1-10.

BJORVATN, B. & URSIN, R. 1998. Changes in sleep and wakefulness following 5-HT1A ligands given systemically and locally in different brain regions. *Rev Neurosci.* 9(4):265-73.

BUENDIA, I., NAVARRO, E., EGEA, J., PARADA, E., GÓMEZ, V., CASAS, I., LAUDON, M., LEÓN, R. & LÓPEZ, M. G. Neuroprotective mechanism of the novel melatonin derivative Neu-P11 against oxygen and glucose deprivation in rat hippocampal slices and in vivo fotothrombotic stroke model. Spanish congress of pharmacology FARMADRID XXIII, 2014 Madrid.

BUYSSE, D. J., REYNOLDS, C. F., 3RD, MONK, T. H., BERMAN, S. R. & KUPFER, D. J. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28(2):193-213.

CARPENTER, B. D., STRAUSS, M. & PATTERSON, M. B. 1996. Sleep disturbances in community-dwelling patients with Alzheimer's disease. *Clin Gerontol.* 16(2):35-49.

CHUNG, S. D., LIN, C. C., WANG, L. H., LIN, H. C. & KANG, J. H. 2013. Zolpidem use and the risk of injury: a population-based follow-up study. *PLoS One.* 8(6):e67459.

CUMMINGS, J., MEGA, M., GRAY, K., ROSENBERG-THOMPSON, S., CARUSI, D. & GORNBEIN, J. 1994. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* 44(12):2308-14.

DIEM, S. J., EWING, S. K., STONE, K. L., ANCOLI-ISRAEL, S., REDLINE, S., ENSRUD, K. E. & THE OSTEOPOROTIC FRACTURES IN MEN (MrOS) STUDY Group, 2014. Use of non-benzodiazepine sedative hypnotics and risk of falls in older men. *J Gerontol Geriatr Res.* 3(3):158.

DUTHEY, B. 2013. *Alzheimer disease and other dementias,* EU, Universiteit Utrecht; Boston University; World Health Organization.

ECONOMOU, N., PAPAGEORGIOU, S., BOANAKIS, A., MAESTRI, M., TOGNONI, G. & BONANNI, E. 2013. From normal elderly through mild cognitive impairment (MCI) to Alzheimer's disease. A progression based on sleep polysomnographic findings. *Sleep Medicine.* 14:e19-e20.

FAVA, M., TARGUM, S. D., NIERENBERG, A. A., BLEICHER, L. S., CARTER, T. A., WEDEL, P. C., HEN, R., GAGE, F. H. & BARLOW, C. 2012. An exploratory study of

combination buspirone and melatonin SR in major depressive disorder (MDD): a possible role for neurogenesis in drug discovery. *J Psychiatr Res.* 46:1553-63.

GALASKO, D., BENNET, D., SANO, M., MARSON, D., KAYE, J. & EDLAND, S. 2006. Alzheimer's Disease Cooperative Study. ADCS Prevention Instrument Project: assessment of instrumental activities of daily living for community-dwelling elderly individuals in dementia prevention clinical trials. *Alzheimer Dis Assoc Disord.* 20:s152-69.

GOLD, C. A. & BUDSON, A. E. 2008. Memory loss in Alzheimer's disease: implications for development of therapeutics. *Expert Rev Neurother.* 8(12):1879-91.

GOLD, D. A. 2012. An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *J Clin Exp Neuropsychol.* 34(1):11-34.

GOLD, M. 2007. Study design factors and patient demographics and their effect on the decline of placebo-treated subjects in randomized clinical trials in Alzheimer's disease. *J Clin Psychiatry.* 68(3):430-8.

GRANDY, J. K. 2013. Melatonin: therapeutic intervention in mild cognitive impairment and Alzheimer's disease. *J Neurol Neurophysiol.* 4(2):1000148.

GREENBERG, B. D., CARRILLO, M. C., RYAN, J. M., GOLD, M., GALLAGHER, K., GRUNDMAN, M., BERMAN, R. M., ASHWOOD, T. & SIEMERS, E. R. 2013. Improving Alzheimer's disease phase II clinical trials. *Alzheimers Dement.* 9(1):39-49.

GRUNDMAN, M., PETERSEN, R. C., FERRIS, S. H., THOMAS, R. G., AISEN, P. S., BENNETT, D. A., FOSTER, N. L., JACK, C. R., JR., GALASKO, D. R., DOODY, R., KAYE, J., SANO, M., MOHS, R., GAUTHIER, S., KIM, H. T., JIN, S., SCHULTZ, A. N., SCHAFER, K., MULNARD, R., VAN DYCK, C. H., MINTZER, J., ZAMRINI, E. Y., CAHN-WEINER, D., THAL, L. J. & ALZHEIMER'S DISEASE COOPERATIVE STUDY. 2004. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol.* 61(1):59-66.

HALL-PORTER, J. M., SCHWEITZER, P. K., EISENSTEIN, R. D., AHMED, H. A. H. & WALSH, J. K. 2014. The effect of two benzodiazepine receptor agonist hypnotics on sleep-dependent memory consolidation. *J Clin Sleep Med.* 10:27-34.

HARRISON, J., MINASSIAN, S., JENKINS, L., BLACK, R.S., KOLLER, M. & GRUNDMAN, M. 2007. A neuropsychological test battery for use in Alzheimer disease clinical trials. *Arch Neurol.* 64(9):1323-29.

HE, P., OUYANG, X., ZHOU, S., YIN, W., TANG, C., LAUDON, M. & TIAN, S. 2013. A novel melatonin agonist Neu-P11 facilitates memory performance and improves cognitive impairment in a rat model of Alzheimer' disease. *Horm Behav.* 64(1):1-7.

HUANG, Y., POTTER, R., SIGURDSON, W., ET AL. 2012. EFfects of age and amyloid deposition on aβ dynamics in the human central nervous system. *Arch Neurol.* 69(1):51-58.

ISLAM, M. R., MORIGUCHI, S., TAGASHIRA, H. & FUKUNAGA, K. 2014. Rivastigmine improves hippocampal neurogenesis and depression-like behaviors via 5-HT1A receptor stimulation in olfactory bulbectomized mice. *Neuroscience.* 272:116-30.

KLINE, A. E., MASSUCCI, J. L., DIXON, C. E., ZAFONTE, R. D. & BOLINGER, B. D. 2004. The therapeutic efficacy conferred by the 5-HT(1A) receptor agonist 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) after experimental traumatic brain injury is not mediated by concomitant hypothermia. *J Neurotrauma.* 21(2):175-85.

LAUDON, M., KATZ, A., METZGER, D., STANER, L., PROSS, N., CORNETTE, F., GUICHARD, N., NIR, T. & ZISAPEL, N. 2012. Tolerability, pharmacokinetic and pharmacodynamic evaluation of multiple ascending doses of Neu-P11 in insomnia patients. *Sleep.* 35:A221.

LIU, Y. Y., YIN, D., CHEN, L., QU, W. M., CHEN, C. R., LAUDON, M., CHENG, N. N., URADE, Y. & HUANG, Z. L. 2014. Piromelatine exerts antinociceptive effect via melatonin, opioid, and 5HT1A receptors and hypnotic effect via melatonin receptors in a mouse model of neuropathic pain. *Psychopharmacology (Berl).* 231(20):3973-85.

LUCEY, B. P. & BATEMAN, R. J. 2014. Amyloid-β diurnal pattern: possible role of sleep in Alzheimer's disease pathogenesis. *Neurobiol Aging*. 35:S29-34.

MANDER, B. A., MARKS, S. M., VOGEL, J. W., RAO, V., LU, B., SALETIN, J. M., ANCOLI-ISRAEL, S., JAGUST, W. J. & WALKER, M. P. 2015. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci*. 18(7):1051-7.

MCCURRY, S. M., LOGSDON, R. G., TERI, L., GIBBONS, L. E., KUKULL, W. A., BOWEN, J. D., MCCORMICK, W. C. & LARSON, E. B. 1999. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. *J Geriatr Psychiatry Neurol.* 12(2):53-9.

MCKHANN, G. M., KNOPMAN, D. S., CHERTKOW, H., HYMAN, B. T., JACK, C. R., JR., KAWAS, C. H., KLUNK, W. E., KOROSHETZ, W. J., MANLY, J. J., MAYEUX, R., MOHS, R. C., MORRIS, J. C., ROSSOR, M. N., SCHELTENS, P., CARRILLO, M. C., THIES, B., WEINTRAUB, S. & PHELPS, C. H. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7(3):263-9.

MCKINNON, A., TERPENING, Z., HICKIE, I. B., BATCHELOR, J., GRUNSTEIN, R., LEWIS, S. J. G. & NAISMITH, S. L. 2014. Prevalence and predictors of poor sleep quality in mild cognitive impairment. *J Geriatr Psychiatry Neurol.* 27(3):204-11.

MENDELSOHN, A. R. & LARRICK, J. W. 2013. Sleep facilitates clearance of metabolites from the brain: glymphatic function in aging and neurodegenerative diseases. *Rejuvenation Res.* 16(6):518-23.

MERICA, H., BLOIS, R. & GAILLARD, J. M. 1998. Spectral characteristics of sleep EEG in chronic insomnia. *Eur J Neurosci.* 10(5):1826-34.

MIYATA, S., NODA, A., IWAMOTO, K., KAWANO, N., OKUDA, M. & OZAKI, N. 2013. Poor sleep quality impairs cognitive performance in older adults. *J Sleep Res.* 22:535-41.

MONTI, J. M. & MONTI, D. 2000. Role of dorsal raphe nucleus serotonin 5-HT1A receptor in the regulation of REM sleep. *Life Sci.* 66(21):1999-2012.

MURAKI, Y., YAMANAKA, A., TSUJINO, N., KILDUFF, T. S., GOTO, K. & SAKURAI, T. 2004. Serotonergic regulation of the orexin/hypocretin neurons through the 5-HT1A receptor. *J Neurosci.* 24(32):7159-66.

PACE-SCHOTT, E.F. & SPENCER, R.M. 2015. Sleep-dependent memory consolidation in healthy aging and mild cognitive impairment. *Curr Top Behav Neurosci*. 25:307-30.

QUERFURTH, H. W. & LAFERLA, F. M. 2010. Alzheimer's disease. *N Engl J Med.* 362:329-44.

RAUCHS, G., PIOLINO, P., BERTRAN, F., DE LA SAYETTE, V., VIADER, F., EUSTACHE, F. & DESGRANGES, B. 2013. Retrieval of recent autobiographical memories is associated with slow-wave sleep in early AD. *Front Behav Neurosci.* 7:114.

RODRÍGUEZ, J. J., NORISTANI, H. N. & VERKHRATSKY, A. 2012. The serotonergic system in ageing and Alzheimer's disease. *Prog Neurobiol.* 99(1):15-41.

ROH, J. H., HUANG, Y., BERO, A. W., KASTEN, T., STEWART, F. R., BATEMAN, R. J. & HOLTZMAN, D. M. 2012. Disruption of the sleep-wake cycle and diurnal fluctuation of β-amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med.* 4(150):150ra122.

SANO, M., RAMAN, R., EMOND, J., THOMAS, R. G., PETERSEN, R., SCHNEIDER, L. S. & AISEN, P. S. 2011. Adding delayed recall to the Alzheimer Disease Assessment Scale is useful in studies of mild cognitive impairment but not Alzheimer disease. *Alzheimer Dis Assoc Disord.* 25:122-7.

SCHNEIDER, L.S., OLIN, J.T., DOODY, R.S., CLARK, C.M., MORRIS, J.C., REISBERG, B., SCHMITT, F.A., GRUNDMAN, M., THOMAS, R.G. & FERRIS, S.H. 1997. Validity and reliability of the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord.* 11:22-32.

SCHNEIDER, L. S., CLARK, C. M., DOODY, R., FERRIS, S. H., MORRIS, J. C., RAMAN, R., REISBERG, B. & SCHMITT, F. A. 2006. ADCS Prevention Instrument Project: ADCS-clinicians' global impression of change scales (ADCS-CGIC), self-rated and study partner-rated versions. *Alzheimer Dis Assoc Disord.* 20:S124-38.

SELKOE, D. J. 2002. Alzheimer's disease is a synaptic failure. *Science.* 298(5594):789-91.

SEVIGNY, J. J., PENG, Y., LIU, L. & LINES, C. R. 2010. Item analysis of ADAS-Cog: effect of baseline cognitive impairment in a clinical AD trial. *Am J Alzheimers Dis Other Demen.* 25(2):119-24.

SPIRA, A. P., GAMALDO, A. A., AN, Y., WU, M. N., SIMONSICK, E. M., BILGEL, M., ZHOU, Y., WONG, D. F., FERRUCCI, L. & RESNICK, S. M. 2013. Self-reported sleep and β-amyloid deposition in community-dwelling older adults. *JAMA Neurol.* 70(12):1537-43.

TABUCHI, S., TSUNEMATSU, T., KILDUFF, T. S., SUGIO, S., XU, M., TANAKA, K. F., TAKAHASHI, S., TOMINAGA, M. & YAMANAKA, A. 2013. Influence of inhibitory serotonergic inputs to orexin/hypocretin neurons on the diurnal rhythm of sleep and wakefulness. *Sleep.* 36(9):1391-404.

TANG, S., WANG, L., TIAN, S., DENG, H., LAUDON, M. & QIAO, G. 2012. Effects of Neu-P11 on sodium azide induced memory deficit in rats. *Journal of Heinan Medical University.* 9:1166-9.

TIAN, S. W., LAUDON, M., HAN, L., GAO, J., HUANG, F. L., YANG, Y. F. & DENG, H. F. 2010. Antidepressant- and anxiolytic effects of the novel melatonin agonist Neu-P11 in rodent models. *Acta Pharmacol Sin.* 31(7):775-83.

VITIELLO, M. V. & BORSON, S. 2001. Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. *CNS Drugs.* 15:777-96.

VITIELLO, M. V., PRINZ, P. N., WILLIAMS, D. E., FROMMLET, M. S. & RIES, R. K. 1990. Sleep disturbances in patients with mild-stage Alzheimer's disease. *J Gerontol.* 45(4):M131-8.

WADE, A. G., FARMER, M., HARARI, G., FUND, N., LAUDON, M., NIR, T., FRYDMAN-MAROM, A. & ZISAPEL, N. 2014. Add-on prolonged-release melatonin

for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. *Clin Interv Aging.* 9:947-61.

WESTERBERG, C. E., MANDER, B. A., FLORCZAK, S. M., WEINTRAUB, S., MESULAM, M. M., ZEE, P. C. & PALLER, K. A. 2012. Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. *J Int Neuropsychol Soc.* 18(3):490-500.

XIE, L., KANG, H., XU, Q., CHEN, M. J., LIAO, Y., THIYAGARAJAN, M., O'DONNELL, J., CHRISTENSEN, D. J., NICHOLSON, C., ILIFF, J. J., TAKANO, T., DEANE, R. & NEDERGAARD, M. 2013. Sleep drives metabolite clearance from the adult brain. *Science.* 342(6156):373-7.

YAFFE, K. & BOUSTANI, M. 2014. *Benzodiazepines and risk of Alzheimer's disease*. *BMJ.* 9:349.

YALKINOGLU, Ö., ZISAPEL, N., NIR, T., PIECHATZEK, R., SCHORR-NEUFING, U., BITTERLICH, N., OERTEL, R., ALLGAIER, C., KLUGE, A. & LAUDON, M. 2010. Phase-I study of the safety, tolerability, pharmacokinetics and sleep promoting activity of Neu-P11, a novel putative insomnia drug in healthy humans. *Sleep.* 33:A220.