Statistical Analysis Plan for Interventional Studies
Text only

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Protocol Number: NEUP11-7(PIROAD)

Protocol Title:
Randomized, delayed start, double blind, parallel group, placebo controlled, multicenter study of piromelatine 20 mg in participants with mild dementia due to Alzheimer's disease

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Revision History

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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Table of Contents

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CRF	Case Report Form
ECG	Electrocardiogram
GGT	Gamma-Glutamyltransferase
ICH	International Conference on Harmonization
IWRS	Interactive Web Randomization System
LOTE	Lack of Therapeutic Efficacy
Max	Maximum
MCI	Mild Cognitive Impairment
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed-effects Maximum likelihood Repeated Measures
MMSE	Mini Mental State Examination
N/A	Not Applicable
NPI	Neuropsychiatric Inventory
PPS	Per Protocol Set
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Analysis Set
TEAE	Treatment-Emergent Adverse Event

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Abbreviation	Description
TFL	Table, Figure and Listing
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The final analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study, and database is locked after all data related edits and queries are resolved.

The main efficacy analysis (blinded) is planned after all participants complete the 26 weeks double blind period. If efficacy is not confirmed, then the study will be ended without completing the extension period.

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3. Study Objectives

3.1. Primary Objective

The primary objective of the study is to compare the effect of piromelatine (20 mg daily) to that of placebo on the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog14) at Week 26 of double-blind treatment.

3.2. Secondary Objective(s)

The key secondary objective is to compare the effect of piromelatine (20 mg) to that of placebo on the Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL) at week 26 of double-blind treatment.

Secondary objectives are:

1. To compare the effect of piromelatine (20 mg daily) to that of placebo on global impression assessed by the ADCS-Clinical Global Impression of Change (CGIC) at Week 26 of double-blind treatment
2. To compare the effect of piromelatine (20 mg) to that of placebo on cognitive aspects of mental function assessed by the Mini-Mental State Examination (MMSE) at Week 26 of the double-blind treatment
3. To compare the safety and tolerability of piromelatine (20 mg) to that of placebo over 26 weeks of double-blind treatment

The other secondary objectives are:

4. To compare the effect of piromelatine (20 mg) to that of placebo on behavioral signs and symptoms assessed by the Neuropsychiatric Inventory (NPI) scale after 26 weeks of double-blind treatment
5. To compare the effect of piromelatine (20 mg) to that of placebo on sleep variables derived from the PSQI at Weeks 13, and 26 and over 26 weeks of double-blind treatment
6. To compare the effect of piromelatine (20 mg) to that of placebo on the integrated Alzheimer's Disease Rating Scale (iADRS) after 26 weeks of double-blind treatment

3.3. Exploratory Objective(s)

The exploratory objectives are:

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

3. To compare the effect of piromelatine (20 mg daily) to that of placebo on the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog13/ADAS-cog12/ADAS-cog11) at Week 26 of double-blind treatment safety and efficacy of 18 months piromelatine 20 mg compared to end of the double-blind period.

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4. Study Details/Design

4.1. Brief Description

This study in participants with mild dementia due to Alzheimer's disease is conducted as a confirmatory, randomized efficacy and safety study of 20 mg piromelatine versus placebo in participants who are 2:107,510,000-107,540,000 polymorphism non-carriers and as an exploratory study of potential disease modifying effects of the drug.

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

Patients with a documented history of mild dementia due to AD for at least 12 months, having an MMSE score of 20 to 26 (inclusive) at Screening, and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1 will be recruited and further screened for eligibility. Informant commitment for the study is also necessary.

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

Eligible patients will start a 2-week run-in period with no treatment and 2 weeks period of placebo (single blind), followed by 26 weeks of randomized, double-blind treatment comprising administration of piromelatine or placebo in a 1:1 randomization ratio, for a total treatment duration of 28 weeks. Because of expected differential clinical course and amyloid load, APOE4 carriers randomization will be stratified by APOE4 carrier status measured by the Precivity test.

Visits in the double-blind phase will be carried out at 13 weeks (Visit 3) and 26 weeks (Visit 4) after randomization (Visit 2). There are 3 assessments in the extension period at 39 (Visit 5), 52 (Visit 6) and 78 weeks (Visit 7) after randomization. The informant will be called by study personnel for follow-up and safety and compliance verification purposes (eg, study medication compliance, daylight exposure compliance, and adverse event/concomitant medication checks) on every one week (± 3 days) between

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Visits 2-4 and every two weeks (± 5 days) between visits 5-7. A follow-up phone call to assess adverse events and safety will be completed 2 weeks after the last dose of study medication. An efficacy analysis (blinded) is intended after completion of the 26 weeks double blind period; if efficacy is not confirmed, the study will be terminated without completing the extension period. Patients who discontinue medication treatment prior to Visit 4 (Week 26) will be brought back for a termination visit as soon as possible after termination and not later than week 26.

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

The study consists of a 4-week run-in period of 2 weeks without treatment and 2 weeks 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. An extension period will follow of open label piromelatine 20 mg for 12 months to evaluate potential disease modifying effects.

A follow-up phone call to elicit any adverse events and safety concerns will be completed 2 weeks after the last dose of study medication.

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4.2. Subject Selection

Male or female patients with mild AD dementia who meet the core clinical research criteria of the NIA-AA framework (McKhann, Knopman et al. 2011)

The diagnostic criteria require that patients must exhibit impairments in both cognitive and functional domains for probable AD with documented evidence of progression of disease to be recruited.

First inclusion criteria is: Male and female patients between the ages of 60 and 85 (inclusive) with mild AD. All details about inclusion/exclusion criteria are displayed in protocol.

4.2.1. Inclusion Criteria

The inclusion criteria are defined in Section 11.1.2 of the protocol.

4.2.2. Exclusion Criteria

The exclusion criteria are defined in Section 11.1.3 of the protocol.

4.3. Determination of Sample Size

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

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

Assuming a 25% screen failure rate and 25% 2:107,510,000-107,540,000 polymorphism carriers, 400 patients should be screened in order to randomly assign 224 participants. Assuming 26% withdrawal, 166 patients are expected to complete the 26 weeks study. Allowing for another 24% patient withdrawal during the open-label long term study, 126 patients will complete the 80 weeks period.

4.4. Treatment Assignment and Blinding

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

Active Medication

Piromelatine 20 mg tablets

Placebo Medication

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

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

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

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

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

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

The randomization list will be generated using a computer-based system and randomization will be performed using an interactive web response system (IWRS). The system is RTSM.

The lead statistician will create a dummy randomization and will be used to provide the dry run of Table, Figure and Listing (TFL) outputs before database lock. An independent unblinded statistician, who will not communicate with the sponsor or other interested party, will create the actual randomization. This will be stored in a restricted folder where only the unblinded statistician will have access to.

Unblinding will occur after database lock. The lead statistician will receive the unblinded randomization list from the unblinded team and rerun all the TFL outputs using this list.

4.5. Administration of Study Medication

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.

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4.6. Study Procedures and Flowchart

Table 10.1: Schedule of Assessments

Period	Single-Blind Run-in		Double-Blind placebo-controlled Treatment		Open-label extension (delayed start)			Follow-up [a]	Premature Discontinuation Visit
Visit	1 [b]	2	3	4	5	6	7		
Study Day	–28±5	0 ±5*	91 ± 5	182 ± 5	273± 5	364±5	546±5	560	
Study Week		0	13	26	39	52	78	80	
Explanation of the study	X								
Informed consent - patient	X								
Informed consent - informant	X								
Screening number assigned	X								
Demographic data	X								
Medical and surgical history	X								
CT/MRI [c]	X								
PET/CSF data collection [d]	X								
Inclusion and exclusion criteria	X	X[1]							

Period	Single-Blind Run-in		Double-Blind placebo-controlled Treatment		Open-label extension (delayed start)			Follow-up [a]	Premature Discontinuation Visit
Visit	1 [b]	2	3	4	5	6	7		
Study Day	–28±5	0 ±5[c]	91 ± 5	182 ± 5	273± 5	364±5	546±5	560	
Study Week		0	13	26	39	52	78	80	
Randomization		X							
Physical examination	X		X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	X		X
BMI	X			X			X		
Concomitant medications	X	X	X	X	X	X	X		X
12-lead ECG	X			X			X		X
Hematology/biochemistry/ urinalysis[e]	X		X	X			X		X
Hormonal testing	X			X			X		X
Precivity test[f]	X						X		
Blood sampling for 2:107,510,000-107,540,000 polymorphism [g,h]	X								
Urine drug screen (BZDs and opiates)	X		X		X				
Recording of adverse events		X	X	X	X	X	X	X	X
C-SSRS	X		X	X	X	X	X		X
Compliance verification		X	X	X	X	X	X		
Precivity and 2:107,510,000-107,540,000 polymorphism review		X							
MMSE	X	X		X			X		
ADAS-cog14	X [i]	X	X	X	X	X	X		X
ADCS-CGIC		X	X	X			X		
ADCS-ADL		X	X	X	X	X	X		X
CDR	X	X		X			X		
NPI		X		X			X		
PSQI		X	X	X	X	X	X		
CST Eligibility Review[L]	X								
Study medication dispensed	X	X	X	X	X	X			
Collection of unused study medication and used packs since last visit		X	X	X	X	X	X		X
Run-in phone call [j]	X								
Compliance phone call [k]	On Days (±3) (every week between Visits 2-4 and every 2 weeks (±5) between visits 5-7) [j]								

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

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

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

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

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

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

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

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

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

[h] Retrospective genetic information could be used.

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[i] Practice session

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

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

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

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5. Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in ADAS-cog14 after 26 weeks of double blind treatment.

ADAS-cog14 at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period will be descriptively summarized

5.2. Secondary Efficacy Endpoints

Efficacy will be further assessed based on the following secondary variables:

- ADCS iADL at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period;
- ADCS-CGIC at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period;
- MMSE at baseline, after 26 weeks of double blind treatment and after 78 weeks after randomization in the extension period;
- NPI at baseline, after 26 weeks of double blind treatment and after 78 weeks after randomization in the extension period;
- PSQI at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period;
- iADRS at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period;

5.3. Exploratory Efficacy Endpoints

The following exploratory efficacy parameters will be summarized descriptively:

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

- Disease modifying potential comparing:

a) Difference from baseline in mean ADAS-cog14 scores in the early and delayed start groups by 52 and 78 weeks of treatment.

b) Difference from baseline in mean MMSE, CDR_SB scores in the early and delayed start groups by 78 weeks of treatment.

c) Rate of progression in the 26 weeks extension period and the first 26 weeks randomized period for each group (ADAS cog14, MMSE, ADCS iADL).

- To compare the effect of piromelatine (20 mg daily) to that of placebo on the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog13/ADAS-cog12/ADAS-cog11) at Week 26 of double-blind treatment safety and efficacy of 18 months piromelatine 20 mg compared to end of the double-blind period.

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- The primary efficacy endpoint separated for ApoE4 carriers and non-carriers (see Section 7.7);
- The primary efficacy endpoint separated for insomnia and non-insomnia patients (see Section 7.7);
- The primary efficacy endpoint separated for patients with APS 37 and more and patients with APS 0-36 (see Section 7.7).

5.4. Safety Endpoints

The following variables will be collected for assessment of safety and summarized descriptively or listed:

- Adverse events (including Serious Adverse Events [SAEs]);
- Physical examination;
- Vital signs(heart rate and blood pressure);
- Concomitant medications;
- Laboratory parameters (hematology, biochemistry and urinalysis);
- Electrocardiograms (12-lead ECG);
- C-SSRS.

Secondary Safety Endpoint:

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

Exploratory Safety Endpoint:

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

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6. Analysis Sets

All the primary, secondary and exploratory efficacy endpoints will be analyzed using the full analysis set. The per protocol set will also be used for the analysis of the primary and secondary efficacy endpoints. Safety and tolerability will be analyzed using the safety analysis set.

6.1. Screened Set

The screened set will include all patients screened who have given written informed consent. Unless specified otherwise, this set will be used for the listing and summarization of subject disposition, and for the listing of patient eligibility.

6.2. Safety Set

The safety analysis set (SS) will include all randomized patients who have taken at least one dose of study medication. Patients will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints and for the presentation of patients in all subject listings, with the exception of disposition and eligibility.

6.3. Full Analysis Set

The full analysis set (FAS) 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. Patients will be analyzed according to randomized treatment. The FAS will be used for all analyses of primary, secondary and exploratory efficacy endpoints and for the summarization of demographics and baseline characteristics data.

6.4. Per Protocol Set

The per protocol set (PPS) will include all patients in the full analysis set who have no major protocol violations to be determined at the Blinded Data Review Meeting (BDRM). Patients will be analyzed according to randomized treatment. The PPS will be used for all analyses of primary and secondary efficacy endpoints.

6.5. Protocol Deviations

A protocol deviation is any change or alteration from the procedures stated in the study protocol, consent document, recruitment process, or study materials (e.g., questionnaires).

A major protocol violation is a deviation that has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study. Major protocol violations include (but are not limited to): deviation from inclusion/exclusion criteria, withdrawal criteria met during the study but subject was not withdrawn, prohibited concomitant medications, substantial deviations from the dosing schedule.

A minor protocol violation is a deviation that does not impact subject safety, compromise the integrity of the study data, or affect the subject's willingness to participate in the study.

Protocol deviations will be captured by the clinical monitoring team on an ongoing basis throughout the study and recorded in the clinical trial management system (CTMS) as outlined in the latest version of the Protocol Deviation and Non-compliance Management Plan. These deviations will be discussed in a case-by-case process and classified into major and minor violations before the data base lock at the BDRM.

All protocol deviations will be summarized by major/minor violations (defined within the BDRM) and classification for each treatment group for the safety analysis set.

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All protocol deviation/violation data will be listed on the safety analysis set.

7. General Aspects for Statistical Analysis

7.1. General Methods

This section describes analytical analysis issues that relate to all or some of the analytic analysis sections that follow. It describes general guidelines for analysis as well as the following items:

- SAS version 9.4 or higher will be used.
- Unless otherwise specified, summaries will be presented for each treatment and overall.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- All relevant subject data will be included in listings. All patients entered into the database, including screen failures, will be included in the disposition listings. Patients who are screened only (who have given signed written informed consent) will be presented as a separate group at the end of the appropriate listings.
- Multiple assessments at a given time point (planned, repeat, and unscheduled) will not be included in summary tables unless specified otherwise, but will be included in the listings. For example if there are multiple laboratory results at a given visit/time point, the latest non-missing value within the visit/time point window will be used. See the specific sections of the SAP for further descriptions.
- Comparison between treatment groups are calculated as Piromelatine versus Placebo.
- 2-sided p-values are presented with 3 decimal places.
- Any rounding will be done after all calculations are made.

7.2. Key Definitions

For the purposes of this study, the term “study drug” refers to piromelatine or placebo.

The study day is the day relative to the date of first dose of study drug, where day -1 is the day before the first dose of study drug and day 1 is the day of first dose of study drug (Week 0 (Visit 2)).

The last dose date is defined as the last non-missing date where a nonzero dose of study drug was recorded.

Unless otherwise specified, Week 0 is Visit 2 (after 2 weeks without treatment and 2 weeks single blind placebo) and the data measured at Visit 2 is the baseline measurements. If we have missing assessment at Visit 2, screening visit assessment will be used for the analysis of change from BL. For laboratory data and ECG, data measured at Screening Visit is the baseline measurements and will be used for change from BL. Baseline is the last non-missing observation in corresponding visit windows before the start of the study drug.

7.3. Missing Data

In cases where the baseline value for ADAS-cog14 are missing, values obtained at Screening will be taken and used for analysis.

Pattern mixture model imputation will be used to treat missing data for analyses of covariance (ANCOVA) as described in Section 9.1 and 9.2.1.

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Missing data for AEs where toxicity and relationship to study drug are missing will be treated as described in Section 10.1.

Missing or partial dates for concomitant medications and adverse events will be treated as described in Sections 8.5.2 and 10.1 respectively.

No other imputation of missing data shall be performed.

7.4. Visit Windows

Visit windows will be defined by the flow chart (see section 4.6).

7.5. Pooling of Centers

It was decided on Admendment1 20MAR2022 to no more taken into account centers as part of the model. Section 17.3.5 related to pooling center from this amendement ("For all ANCOVA and MMRM models… by a random-number Generator") is no more used.

7.6. Statistical assumptions

The inherent assumption of normally distributed data will be evaluated by generating output for the residuals from the full MMRM and ANCOVA 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.

7.7. Subgroups

The effect of ApoE4, Amyloid Probability Score (APS) and baseline insomnia severity, upon efficacy will be evaluated if sample sizes are sufficient to warrant such analyses.

Additional subgroups will be determined according to ApoE4 carrier status (the presence of ApoE4 allele), baseline insomnia severity (patients being below or above the PSQI cutoff score of ≥5) and APS (APS 37 and more (intermediate +Consistent with presence of amyloid plaques) / APS 0-36 (Consistent with absence of amyloid plaques)) . These evaluations will be applied to the primary efficacy endpoint for the FAS using the MMRM model.

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8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

All patients who provide informed consent will be accounted for in this study.

The overall number of screened patients who have given written informed consent will be summarized for the screened set.

Patient disposition will be summarized for the screened set.

The study discontinuation along with the reasons for discontinuation as recorded on the eCRF, and the study day of discontinuation will be listed.

The study disposition summary tables will include the number and percentage of patients in each of the analysis sets and the reason for study discontinuation. Patients who are screen failures will be included in the all patients column.

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

Subject disposition data will be listed on the screened set.

8.2. Demographic and Baseline Characteristics

Demographic data (age, gender, BMI), education (years), duration of AD, severity of disease as expressed by MMSE score, β-amyloid 42/40 , Amyloid Probability Score (APS) and ApoE4 genotyping will be summarized by treatment group for the full analysis set using descriptive statistics. No formal statistical testing will be performed on these data.

Age (years) will be calculated as the number of years between the date of birth and the date informed consent was recorded on the eCRF.

Age at Screening = (informed consent date - date of birth + 1) / 365.25 and truncated to complete years.

8.3. Medical History and Concomitant Diseases

Medical/surgical history as recorded at Screening (Visit 1) will be summarized using the full analysis set by treatment group using the number and percentage of patients reporting each system organ class (SOC) and preferred term (PT). Medical/surgical history will be sorted by descending overall total by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 25 or later in the summary table.

Medical/surgical history data will be listed on the safety analysis set and sorted by treatment group, patient number, onset date, SOC, and PT.

8.4. Other Baseline Characteristics

Duration of AD and severity of insomnia as expressed by PSQI score at baseline will be summarized by treatment group using the full analysis set.

Duration of AD will be calculated as:

(Date of informed consent – onset date of AD) / 365.25 and displayed to 1 decimal place.

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For the calculation 01JAN will be imputed as only onset year of AD is recorded. Duration of AD and severity of disease will be summarized using summary statistics for continuous variables.

Optional ApoE4 genotyping will be summarized using the full analysis set. Subjects will be classified as ApoE4 carriers if they will have one or more copies of the ApoE4 allele. That is, subjects of the genotypes e4/e4, e4/e3 and e4/e2. Subjects without the ApoE e4 allele will be classified as Non-carriers (i.e., e3/e3, e3/e2, and e2/e2). This definition will be used for the subgroup exploratory analysis.

Severity of insomnia will be determined using a score cutoff of ≥5 in PSQI global score for insomnia at baseline. This definition will be used for the subgroup analysis.

APS (Amyloid Probability Score) will be summarized using the full analysis set. Subjects will be classified as APS 37 and more (intermediate +Consistent with presence of amyloid plaques) / APS 0-36 (Consistent with absence of amyloid plaques).. This definition will be used for the subgroup exploratory analysis.

This will be summarized post data base lock (DBL) once the data is analyzed.

All data will be listed on the full analysis set.

8.5. Medication

A summary of medications taken during the course of the study will be presented in tabular form using Anatomical Therapeutic Chemical (ATC) classification level 2 and PT via the World Health Organization Drug classification Dictionary (WHO-DD) version March 2022 or later. All medications will be summarized using the full analysis set by treatment group and sorted alphabetically by ATC level 2 class and PT.

8.5.1. Prior Medication

Prior medications are those medications taken before the start of treatment in the run-in phase, not including medications ongoing at the start of the run-in.

8.5.2. Concomitant Medication

A medication is considered concomitant in the run-in phase if ongoing at or taken on or after the start date of treatment in the run-in.

A medication is considered concomitant in the double-blind treatment phase if ongoing at or taken on or after the start date of study treatment.

A medication can be concomitant in both the run-in and double-blind treatment phases.

Concomitant medications will be summarized by the number and percentage of patients taking a particular medication using the coding described above by phase. If a patient has taken a medication more than once, the patient will be counted only once in the total. Prior medications will be listed only.

See Section 12.9 of the protocol for more details on the time frame allowed for medications.

Medications with incomplete end dates will be considered concomitant, unless an incomplete date (e.g. month and year) clearly indicates that the medication started and stopped prior to the start of treatment:

- Day and month are missing and the year is equal to or after the year of the start of treatment in the run-in;
- Day is missing and the year is after the year of the start of treatment in the run-in;
- Day is missing and the year is equal to the year of the start of treatment in the run-in and the month is equal to or after the month of the start of the run-in;
- Year is missing; or
- Complete date is missing.

8.6. Extent of Exposure

The duration of exposure (in days) to study medication will be summarized using summary statistics for continuous variables. This will be calculated using the safety analysis set.

Duration of exposure will be calculated by:

Date of last dose – date of first dose + 1

The study medication accountability will be listed along with the duration of exposure.

8.7. 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.

Compliance to study medication will be summarized using summary statistics for continuous variables for each visit and overall. This will be calculated using the full analysis set.

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9. Efficacy

9.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is the change from Baseline in ADAS-cog14 after 26 weeks of double blind treatment.

The ADAS-cog 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 cancellation, 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.

The ADAS-cog14 global score will be summarized at baseline and after 13, and 26 weeks of double-blind treatment (actual and change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum), and after 39, 52 and 78 weeks after randomization in the extension period.

The primary efficacy analysis will be carried out using an analysis of covariance (ANCOVA) method where the change in ADAS-cog14 scores from baseline to Week 26 (Visit 4) will be the outcome variable and treatment group will be main effects. The ADAS-cog14 scores at baseline and ApoE4 will be included as covariates. Baseline will be the last non-missing observation at Visit 2 or before. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

Missing data will be imputed using a pattern mixture model approach. Four patterns of missing data will be considered and imputed independently as follows:

- Pattern 1: will include patients who completed treatment on study drug (any missing data here is considered missing at random);
- Pattern 2: will include patients who discontinue treatment early due to adverse events (AEs);
- Pattern 3: will include patients who discontinue treatment early due to lack of therapeutic efficacy (LOTE);
- Pattern 4: will include patients who discontinue treatment early due to reasons other than AE event or LOTE.

The pattern mixture model methodology will be implemented using SAS procedures MI and MIANALYZE. Specifically, the following steps will be followed:

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data for patients who discontinue early will be multiply imputed as follows:

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- If the patient discontinues due to an AE (Pattern 2) or LOTE (Pattern 3), then missing data will be assumed to follow a distribution similar to the baseline values observed in the placebo arm of the study;

- If the patient discontinues due to reasons other than an AE or LOTE (Pattern 4), at each time point, missing data will be assumed to follow a distribution similar to scores for patients that are still in the study and randomized to the same treatment group.

- Results of the ANCOVA on the multiply imputed data will be summarized using the SAS procedure MIANALYZE.

Change in ADAS-cog14 scores from baseline over Week 26 (Visit 4) will be also analyzed using a MMRM model utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model will include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and ApoE4 as covariates. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

9.2. Secondary Efficacy Endpoints and Analyses

9.2.1. Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale

ADCS iADL at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period will be analysed.

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

The ADCS-iADL global scores and changes from baseline will be summarized (by treatment) at each visit.

Change in ADCS-iADL scores from baseline to Week 26 (Visit 4) will be analyzed using a MMRM model utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model will include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and ApoE4 as covariates. The treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2. The standard

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error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

Efficacy analysis will be also carried out using an ANCOVA method where the change in ADCS-ADL scores from baseline to Week 13 (Visit 3) and Week 26 (Visit 4) will be the outcome variable and treatment group will be main effects. The ADCS-ADL scores at baseline and ApoE4 will be included as covariates. Multiple imputation for missing values will take place using the pattern mixture model approach, as described in Section 9.1. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

9.2.2. Clinical Global Impression of Change

ADCS-CGIC at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period will be analysed.

The ADCS-CGIC is a systematic method for assessing clinically significant change in a clinical trial as viewed by an independent skilled and experienced clinician. The ADCS-CGIC focuses on clinicians' observations of change in the patient's cognitive, functional, and behavioral performance since the beginning of a trial. It relies on both direct examination of the patient and interview of informants. Unlike a targeted symptom scale, it takes into account a patient's overall function in the cognitive, behavioral, and functional activity domains. Scoring is based on an interview with the informant and examination of the patient by an independent evaluator, without consulting other information such as cognitive test results. The ADCS-CGIC requires the assessor to consider a number of cognitive, functional, and behavioral areas prior to providing an overall "global" assessment of clinical change.

The CGIC is a single score with ordered values of 1 to 7 for “marked improvement” to “marked worsening”. A negative change from baseline indicates an improvement.

The CGIC scores will be summarized (by treatment) at each visit.

MMRM model will be used to analyze CGIC, utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. The treatment difference estimates at each visit will be reported, with 95% confidence intervals and P values.

Efficacy analysis will be also carried out using an ANCOVA method where the CGIC Week 13 (Visit 3) and Week 26 (Visit 4) will be the outcome variable and treatment group will be main effects. The CGIC score at baseline and ApoE4 will be included as covariates. The standard error will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

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These analyses will be performed on the full analysis set and additionally on the per protocol set as a supportive analysis.

9.2.3. Mini Mental State Examination

MMSE at baseline, after 26 weeks of double blind treatment and after 78 weeks after randomization in the extension period will be analysed.

The MMSE is a brief assessment instrument used to assess cognitive function in elderly patients. 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.

MMRM model will be used to analyze MMSE, utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. The treatment difference estimates at each visit will be reported, with 95% confidence intervals and P values.

Change in MMSE global scores from baseline to Week 26 (Visit 4) will be analyzed using an ANCOVA method where the change in MMSE scores from baseline to Week 26 will be the outcome variable and treatment group will be main effects. MMSE scores at baseline and ApoE4 will be included as covariates. Baseline will be the last non-missing observation at Visit 2. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

9.2.4. Neuropsychiatric Inventory

NPI at baseline, after 26 weeks of double blind treatment and after 78 weeks after randomization in the extension period will be analysed.

The NPI 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).

MMRM model will also be used to analyze NPI, utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. The treatment difference estimates at each visit will be reported, with 95% confidence intervals and P values.

Change in the NPI individual items and global scores from baseline to and Week 26 (Visit 4) will be analyzed using an ANCOVA method, where the change in the NPI scores from baseline to Week 26 will be the outcome variable and treatment group will be main effects. The NPI scores at baseline and ApoE4 will be

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included as covariates. Baseline will be the last non-missing observation at Visit 2. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

The distress score shall be listed only.

9.2.5. Pittsburgh Sleep Quality Index

PSQI at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period will be analysed.

The PSQI is an effective instrument used to measure the quality and patterns of sleep in older adults. It differentiates “poor” from “good” sleep by measuring 7 areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The patient self-rates each of these 7 areas of sleep. Scoring of answers is based on a 0 to 3 scale, where a score of 3 reflects the negative extreme on the Likert Scale. A global sum of 5 or greater indicates a “poor” sleeper.

Change in the PSQI, for each of the 7 individual components, questions 2 and 4, and the global scores from baseline will be summarized (by treatment) at each visit.

MMRM model will also be used to analyze PSQI, utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. The treatment difference estimates at each visit will be reported, with 95% confidence intervals and P values.

Change in PSQI scores (individual components and global) from baseline to Week 13 (Visit 3) and Week 26 (Visit 4) will be analyzed using an ANCOVA method where the change in the PSQI scores from baseline to Week 13, or Week 26 will be the outcome variable and treatment group will be main effects. The PSQI scores at baseline and ApoE4 will be included as covariates. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

9.2.6. integrated Alzheimer’s Disease Rating Scale

iADRS at baseline, after 13, and after 26 weeks of double blind treatment and after 39, 52 and 78 weeks after randomization in the extension period will be analysed.

The integrated Alzheimer’s Disease Rating Scale (iADRS) combines scores from the 2 widely accepted measures, the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and the Alzheimer’s Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL). (iADRS), (Wessels et al., 2015) The iADRS has been shown to perform better than most composites and scales in detecting disease progression and comparably or better than individual scales in detecting treatment differences. The iADRS can be divided into two principal components primarily representing cognitive items and instrumental ADLs. Dynamic ranges of the subscales were similar across all studies, reflecting approximately equal contributions from both subscales to the iADRS total score. In item analyses, every

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item contributed to the total score, with varying strength of contributions by item and across data sets. The iADRS demonstrated acceptable psychometric properties and was effective in capturing disease progression from MCI through moderate AD and treatment effects across the early disease spectrum. These findings suggest the iADRS can be used in studies of mixed populations, ensuring sensitivity to treatment effects as subjects progress during studies of putative disease-modifying agents. In the present study iADRS score will be calculated from the ADAS-cog14 and ADCS-iADL scores using the equation (Wessels, Siemers et al. 2015)

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

Change in iADRS from baseline will be summarized (by treatment) at each visit.

MMRM model will also be used to analyze iADRS, utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model shall include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and APOE genotype as covariates. The treatment difference estimates at each visit will be reported, with 95% confidence intervals and P values.

Change in iADRS from baseline to Week 13 (Visit 3) and Week 26 (Visit 4) will be analyzed using an ANCOVA method where the change in the iADRS from baseline to Week 13, or Week 26 will be the outcome variable and treatment group will be main effects. The iADRS at baseline and ApoE4 will be included as covariates. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

9.3. Exploratory Efficacy Endpoints and Analyses

9.3.1. ApoE4 Carrier Status

An additional exploratory efficacy analysis will be carried out for the primary efficacy endpoint (as detailed in Section 5.1) separately for ApoE4 carriers and non-carriers.

This analysis will be performed on the full analysis set using the MMRM model and will include calculation of an effect size. See Sections 9.1 for the individual analysis.

This analysis will be performed only for patients who have provided their consent to use their genetic material for the analysis of the ApoE gene.

9.3.2. Insomnia at Baseline

An additional exploratory efficacy analysis will be carried out for the primary efficacy endpoint (as detailed in Section 5.1) separately for patients with and without insomnia as determined by the PSQI score obtained at baseline.

This analysis will be performed on the full analysis set using the MMRM model and will include calculation of an effect size. See Sections 9.1 for the individual analyses.

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9.3.3. Amyloid Probability Score at Baseline

An additional exploratory efficacy analysis will be carried out for the primary efficacy endpoint (as detailed in Section 5.1) separately for patients with Amyloid Probability Score: APS 37 and more (intermediate +Consistent with presence of amyloid plaques) / APS 0-36 (Consistent with absence of amyloid plaques).

This analysis will be performed on the full analysis set using the MMRM model and will include calculation of an effect size. See Sections 9.1 for the individual analyses.

9.3.4. Clinical Dementia Rating Sum of Boxes

The Clinical Dementia Rating (CDR) data will be descriptively summarized on the full analysis set for exploratory analysis.

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

9.3.5. Exploratory Efficacy Analyses

The following exploratory efficacy parameters will be summarized descriptively:

- Long-term efficacy of 18 months piromelatine 20 mg compared to end of the double blind period.
- Disease modifying potential comparing:

a) Difference from baseline in mean ADAS-cog14 scores in the early and delayed start groups by 52 and 78 weeks of treatment.

b) Difference from baseline in mean MMSE, CDR_SB (see Section 9.3.4) scores in the early and delayed start groups by 78 weeks of treatment.

c) Rate of progression in the 26 weeks extension period and the first 26 weeks randomized period for each group (ADAS cog14, MMSE, ADCS iADL).

- To compare the effect of piromelatine (20 mg daily) to that of placebo on the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog13/ADAS-cog12/ADAS-cog11) at Week 26 of double-blind treatment safety and efficacy of 18 months piromelatine 20 mg compared to end of the double-blind period.
- The primary efficacy endpoint separated for ApoE4 carriers and non-carriers (see Sections 9.3.1 and 7.7);
- The primary efficacy endpoint separated for insomnia and non-insomnia patients (see Sections 9.3.2 and 7.7);

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- The primary efficacy endpoint separated for patients with APS 37 and more and patients with APS 0-36 (see Sections 9.3.3 and 7.7).

10. Safety

The safety analysis set will be used for the listing of safety data and for all safety analyses.

Safety will be assessed on the basis of adverse event (AE) reports, Vital signs measurements (heart rate and blood pressure), physical examinations, clinical laboratory evaluations (hematology, biochemistry, and urinalysis), 12-lead ECGs, C-SSRS.

No formal statistical testing will be performed on the safety data.

10.1. Adverse Events

Adverse events will be collected throughout the study and will be summarized by the SOC and PT based on the MedDRA dictionary version 25 or later.

Treatment-emergent adverse events (TEAEs) in the double-blind treatment phase are defined as AEs that first occur or worsen in severity after the first administration of study medications. TEAEs during Run-in period are defined as AEs that first occur or worsen in severity after the start date of placebo in the run-in. TEAEs in the open label phase are also defined. The number of patients reporting TEAEs will be summarized during the Run-in period, 26-week treatment period and during the 52 weeks extension period by system organ class system and preferred term for each treatment group.

See Section 14.2 of the protocol for definition of serious adverse events (SAEs).

Treatment emergent AEs will be characterized based on the onset date relative to each patient's participation in the study.

Adverse events with incomplete start dates will be considered a TEAE if:

- Day and month are missing and the year is equal to or after the year of the first dose date;
- Day is missing and the year is after the year of the first dose;
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;
- Year is missing; or
- Complete date is missing.

If the relationship to study treatment is missing then related will be used for the summaries. Similarly, events with missing intensity or severity will be counted as severe (Grade 3).

The summary tables will include the number of subjects and the number of events. Percentages will be based on the number of subjects. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum severity, a patient will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

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The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following AE tables will be provided:

- An overall summary of the number and percentage of patients reporting AEs, TEAEs, treatment-related TEAEs, severe TEAEs, serious TEAEs, treatment-related serious TEAEs, and TEAEs leading to withdrawal of study medication;
- TEAEs, overall and by SOC and PT;
- Serious TEAEs, overall and by SOC and PT;
- TEAEs related to study medication, overall and by SOC and PT;
- TEAEs, overall and by SOC, PT and maximum severity;
- TEAEs leading to withdrawal of study medication, overall and by SOC and PT;
- TEAEs, overall and by PT;
- All AEs, overall and by SOC and PT;
- All AEs, overall and by SOC, PT and maximum severity.

With the exception of the all AEs table, only the TEAEs will be included in the summary tables; however, all AEs will be included in the listings. Any AE occurring during the single-blind run-in, before the first dose of study medication in the double-blind treatment phase, will be included in the summaries of all AEs only. Any AE occurring before the single-blind run-in will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within the defined 14 day follow-up period after discontinuation of study medication will be included in the AE summaries.

With the exception of the all AEs tables, the summaries of TEAEs will present frequency of AEs by SOC and PT, will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

An additional listing will be provided for SAEs leading to withdrawal from the study. TEAEs will be flagged in the listings.

10.2. Laboratory Evaluations

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

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

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

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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, 4, 7 and premature discontinuation visit.

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

10.3. Vital Signs

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

10.4. ECG

A 12-lead ECG will be performed at Visit 1 (Screening), Visit 4 (Week 26), and Visit 7 (Week 78; end-of-study visit).

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

10.5. Physical Examination

Physical examination 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.

10.6. Other Safety

C-SSRS

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

Subsequent change from Screening on the C-SSRS will be summarized by study visit.

The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the patient's lifetime and for each scheduled visit will be presented by actual treatment group. All data will be listed by actual treatment group.

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Details of C-SSRS scoring are described in ***Error! Reference source not found.***).

11. Interim Analyses

The main efficacy analysis (blinded) is planned after all participants complete the 26 weeks double blind period. If efficacy is not confirmed, then the study will be ended without completing the extension period.

Decision will be taken by Sponsor on primary analysis ADAS-Cog 14, on the key secondary analysis ADCS-iADL, and on the ADCS-CGIC for the 26 weeks time point, based on outputs delivered by Syneos Health Biostatistical team. Min/Max, figures, listings won't be shared with Sponsor to keep blinding.

This document is confidential.

12. Changes from Analysis Planned in Protocol

NA

13. Reference List

Nilsson ME, et all (2013). Nilsson ME, Suryawanshi S, Gassmann-Mayer C, Dubrava S, McSorley P, Jiang K. (2013). Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide, https://cssrs.columbia.edu/wp-content/uploads/ScoringandDataAnalysisGuide-for-Clinical-Trials-1.pdf

Wessels, A., E. Siemers, P. Yu, S. Andersen, K. Holdridge, J. Sims, K. Sundell, Y. Stern, D. Rentz, B. Dubois, R. Jones, J. Cummings and P. Aisen (2015). "A Combined Measure of Cognition and Function for Clinical Trials: The Integrated Alzheimer's Disease Rating Scale (iADRS)." J Prev Alzheimers Dis. 2(4): 227-241.

McKhann, G. M., D. S. Knopman, H. Chertkow, B. T. Hyman, C. R. Jack, Jr., C. H. Kawas, W. E. Klunk, W. J. Koroshetz, J. J. Manly, R. Mayeux, R. C. Mohs, J. C. Morris, M. N. Rossor, P. Scheltens, M. C. Carrillo, B. Thies, S. Weintraub and C. H. Phelps (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): 263-269.

This document is confidential.

14. Programming Considerations

All TLFs and statistical analyses are generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure outputs adhere to the following specifications.

14.1. General Considerations

- One SAS program can create several outputs
- Each output will be stored in a separate file
- Output files will be delivered in Word rtf format
- Numbering of TFLs will follow ICH E3 guidance

14.2. Table, Figure, and Listing Format

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output will have the following header at the top of each page:
- Neurim Pharmaceuticals (1991) Ltd Protocol NEUP11-7(PIROAD); (Syneos Health study number 7031211); Draft/Final Run <date>
- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)

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- The date the output was generated will appear along with the program name as a footer on each page

14.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but Sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Safety Analysis Set)

14.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include 'unit' in column or row heading when appropriate
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable)

14.2.5. Body of the Data Display

14.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

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14.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters,all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: ‘0.xxx’, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more

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than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'

- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

14.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time

- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study

- Units will be included where available

14.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display

- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible

- Subject specific footnotes are avoided, where possible

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- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when mutiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

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15. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907) .

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Vaidation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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16. Index of Tables

This document is confidential.

Table 14.2.2.2.8 CGIC Results: Analysis to Week 13 and Week 26 versus Placebo Per Protocol Set
Table 14.2.2.3.1 MMSE Global Results by Visit Full Analysis Set
Table 14.2.2.3.2 MMRM Analysis of MMSE Global Results Full Analysis Set
Table 14.2.2.3.3 MMSE Global Results: Analysis of Change from Baseline to Week 26 versus Placebo Full Analysis Set
Table 14.2.2.3.4 MMSE Global Results by Visit Per Protocol Set
Table 14.2.2.3.5 MMRM Analysis of MMSE Global Results Per Protocol Set
Table 14.2.2.3.6 MMSE Global Results: Analysis of Change from Baseline to Week 26 versus Placebo Per Protocol Set
Table 14.2.2.4.1 NPI Individual Items and Total Scores by Visit Full Analysis Set
Table 14.2.2.4.2 MMRM Analysis of NPI Individual Items and Total Scores Full Analysis Set
Table 14.2.2.4.3 NPI Individual Items and Total Scores: Analysis of Change from Baseline to Week 26 versus Placebo Full Analysis Set
Table 14.2.2.4.4 NPI Individual Items and Total Scores by Visit Per Protocol Set
Table 14.2.2.4.5 MMRM Analysis of NPI Individual Items and Total Scores Per Protocol Set
Table 14.2.2.4.6 NPI Individual Items and Total Scores: Analysis of Change from Baseline to Week 26 versus Placebo Per Protocol Set
Table 14.2.2.5.1 PSQI Individual Items and Globals Score by Visit Full Analysis Set
Table 14.2.2.5.2 MMRM Analysis of PSQI Individual Items and Globals Score Full Analysis Set
Table 14.2.2.5.3 PSQI Individual Items and Global Scores: Analysis of Change from Baseline to Week 13 and Week 26 versus Placebo Full Analysis Set
Table 14.2.2.5.4 PSQI Individual Items and Global Scores by Visit Per Protocol Set
Table 14.2.2.5.5 MMRM Analysis of PSQI Individual Items and Global Scores Per Protocol Set
Table 14.2.2.5.6 PSQI Individual Items and Global Scores: Analysis of Change from Baseline to Week 26 versus Placebo Per Protocol Set
Table 14.2.2.6.1 iADRS Score by Visit Full Analysis Set
Table 14.2.2.6.2 MMRM Analysis of iADRS Score Full Analysis Set
Table 14.2.2.6.3 iADRS Score: Analysis of Change from Baseline to Week 13 and Week 26 versus Placebo Full Analysis Set
Table 14.2.2.6.4 iADRS Score by Visit Per Protocol Set
Table 14.2.2.6.5 MMRM Analysis of iADRS Score Per Protocol Set
Table 14.2.2.6.6 iADRS Score: Analysis of Change from Baseline to Week 13 and Week 26 versus Placebo Per Protocol Set
Exploratory Efficacy Parameters
Table 14.2.3.1.1 ADAS-cog14 Results by Visit: ApoE4 Carrier Status Full Analysis Set
Table 14.2.3.1.2 MMRM Analysis of ADAS-cog14 Results: ApoE4 Carrier Status Full Analysis Set
Table 14.2.3.2.1 ADAS-cog14 Results by Visit: Baseline Insomnia Full Analysis Set
Table 14.2.3.2.2 MMRM Analysis of ADAS-cog14 Results: Baseline Insomnia Full Analysis Set
Table 14.2.3.3.1 ADAS-cog14 Results by Visit: APS Full Analysis Set
Table 14.2.3.3.2 MMRM Analysis of ADAS-cog14 Results: APS Full Analysis Set
Table 14.2.3.4.1 Clinical Dementia Rating Sum of Boxes by Visit Full Analysis Set
Table 14.2.3.5.1 ADAS-cog13, ADAS-cog12 and ADAS-cog11 Results by Visit Full Analysis Set
Table 14.2.3.5.2 MMRM Analysis of ADAS-cog13, ADAS-cog12 and ADAS-cog11 Results Full Analysis Set

This document is confidential.

Table 14.2.3.5.3 ADAS-cog13, ADAS-cog12 and ADAS-cog11 Results: Analysis of Change from Baseline to Week 13 and Week 26 versus Placebo Full Analysis Set
Safety Data
Displays of Adverse Events
Table 14.3.1.1 Overall Summary of All Adverse Events (AEs) Safety Analysis Set
Table 14.3.1.2 Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term Safety Analysis Set
Table 14.3.1.3 Serious Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term Safety Analysis Set
Table 14.3.1.4 Treatment Emergent Adverse Events (TEAEs) Related to Study Medication by System Organ Class and Preferred Term Safety Analysis Set
Table 14.3.1.5 Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term and Maximum Severity Safety Analysis Set
Table 14.3.1.6 Treatment Emergent Adverse Events (TEAEs) Leading to Withdrawal of Study Medication by System Organ Class and Preferred Term Safety Analysis Set
Table 14.3.1.7 Treatment Emergent Adverse Events (TEAEs) by Preferred Term Safety Analysis Set
Table 14.3.1.8 All Adverse Events (AEs) by System Organ Class and Preferred Term Safety Analysis Set
Table 14.3.1.9 All Adverse Events (TEAEs) by System Organ Class, Preferred Term and Maximum Severity Safety Analysis Set
Table 14.3.2.1 Listing of all Serious Adverse Events Leading to Withdrawal from the Study during Double-Blind Treatment and Extension open label periods Safety Analysis Set
Clinical Laboratory Data
Table 14.3.4.1.1.1 Laboratory Results by Visit: Hematology Safety Analysis Set
Table 14.3.4.1.1.2 Shift from Baseline in Laboratory Results by Visit: Hematology Safety Analysis Set
Table 14.3.4.1.2.1 Laboratory Results by Visit: Chemistry Safety Analysis Set
Table 14.3.4.1.2.2 Shift from Baseline in Laboratory Results by Visit: Chemistry Safety Analysis Set
Table 14.3.4.1.3.1 Laboratory Results by Visit: Urinalysis Safety Analysis Set
Table 14.3.4.1.3.2 Shift from Baseline in Laboratory Results by Visit: Urinalysis Safety Analysis Set
Vital Signs
Table 14.3.4.2 Vital Signs by Visit Safety Analysis Set
Electrocardiogram (ECG) Data
Table 14.3.4.3.1 ECG Interval Results by Visit Safety Analysis Set
Table 14.3.4.3.2 Overall Results of 12-Lead ECG by Visit Safety Analysis Set
Physical Examination Results
Table 14.3.4.4 Overall Results of Physical Examination by Visit Safety Analysis Set
C-SSRS
Table 14.3.4.5 Columbia-Suicide Severity Rating Scale (C-SSRS): Summary of most severe assessments by Visit Safety Analysis Set
Extent of Exposure
Table 14.3.4.6 Extent of Exposure Safety Analysis Set

This document is confidential.

17. Index of Figures

NA

18. Index of Listings

Discontinued Subjects
Listing 16.2.1 Subject Disposition Screened Set
Protocol Deviations
Listing 16.2.2 Protocol Deviations Safety Analysis Set
Listing 16.2.3.1 Informed Consent and Subject Eligibility Screened Set
Subjects Excluded from the Efficacy Analysis
Listing 16.2.3.2 Exclusions from Analysis Sets
Listing 16.2.3.3 Randomization Screened Set
Listing 16.2.3.4 Run in Telephone Contact Safety Analysis Set
Demographic Data
Listing 16.2.4.1 Demographic Characteristics and Education Status Safety Analysis Set
Listing 16.2.4.2 Medical/Surgical History Safety Analysis Set
Listing 16.2.4.3.1 Baseline Characteristics - Alzheimer's Disease Safety Analysis Set
Listing 16.2.4.3.2 Baseline Characteristics – ApoE4 Genotyping Safety Analysis Set
Listing 16.2.4.4 Prior and Concomitant Medications Safety Analysis Set
Listing 16.2.4.5 CT/MRI Scan Safety Analysis Set
Listing 16.2.4.6 PET/CSF Scans Safety Analysis Set
Compliance and/or Drug Concentration Data
Listing 16.2.5.1 Study Drug Administration Safety Analysis Set
Listing 16.2.5.2 Study Medication Accountability Safety Analysis Set
Listing 16.2.5.3 Treatment Compliance Safety Analysis Set
Listing 16.2.5.4 Safety and compliance Telephone Call Safety Analysis Set
Individual Efficacy Response Data
Listing 16.2.6.1.1 Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 1 Safety Analysis Set
Listing 16.2.6.1.2 Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 2 Safety Analysis Set
Listing 16.2.6.1.3 Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 3 Safety Analysis Set
Listing 16.2.6.1.4 Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 4 Safety Analysis Set
Listing 16.2.6.1.5 Alzheimer's Disease Assessment Scale Cognitive Subscale-14 Results Part 5 Safety Analysis Set
Listing 16.2.6.1.6 Alzheimer's Disease Assessment Scale Cognitive Subscales Scores Safety Analysis Set
Listing 16.2.6.2.1 Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Safety Analysis Set
Listing 16.2.6.2.2 The integrated Alzheimer's Disease Rating Scale Safety Analysis Set
Listing 16.2.6.3 Clinical Global Impression of Change Safety Analysis Set
Listing 16.2.6.4 Mini Mental State Examination Safety Analysis Set
Listing 16.2.6.5 Neuropsychiatric Inventory Safety Analysis Set
Listing 16.2.6.7 Pittsburgh Sleep Quality Index Safety Analysis Set
Listing 16.2.6.8 Clinical Dementia Rating SB Safety Analysis Set
Adverse Event Listings
Listing 16.2.7.1 All Adverse Events Safety Analysis Set
Listing of individual laboratory measurements by patient

This document is confidential.

Listing 16.2.8.1.1 Laboratory Results: Hematology Safety Analysis Set
Listing 16.2.8.1.2 Laboratory Results: Chemistry Safety Analysis Set
Listing 16.2.8.1.3 Laboratory Results: Hormones (Testosterone, Prolactin) Safety Analysis Set
Listing 16.2.8.1.4 Laboratory Results: Urinalysis Safety Analysis Set
Listing 16.2.8.1.5 Laboratory Results: Urine Drug Screen Safety Analysis Set
Listing of individual other Safety measurements by patient
Listing 16.2.8.2.1 Vital Signs Safety Analysis Set
Listing 16.2.8.2.2 12-Lead ECG Safety Analysis Set
Listing 16.2.8.2.3 Physical Examination Safety Analysis Set
Listing 16.2.8.2.4 Precivity and p-Tau tests Safety Analysis Set
Listing 16.2.8.3.1 Columbia-Suicide Severity Rating Scale (C-SSRS): Baseline/Screening - Suicidal Ideation Safety Analysis Set
Listing 16.2.8.3.2 Columbia-Suicide Severity Rating Scale (C-SSRS): Suicidal Behavior – Baseline/Screening Safety Analysis Set
Listing 16.2.8.3.3 Columbia-Suicide Severity Rating Scale (C-SSRS): Actual Attempts only – Baseline/Screening Safety Analysis Set
Listing 16.2.8.3.4 Columbia-Suicide Severity Rating Scale (C-SSRS): Suicidal Ideation – Since Last Visit Safety Analysis Set
Listing 16.2.8.3.5 Columbia-Suicide Severity Rating Scale (C-SSRS): Intensity of Suicidal Ideation – Since Last Visit Safety Analysis Set
Listing 16.2.8.3.6 Columbia-Suicide Severity Rating Scale (C-SSRS): Suicidal Behavior – since last visit Safety Analysis Set
Listing 16.2.8.3.7 Columbia-Suicide Severity Rating Scale (C-SSRS): Actual Attempts only – since last visit Safety Analysis Set

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19. Appendices

19.1. Appendix 1. ANCOVA with missing data imputation

19.1.1. Extract from SAP

The primary efficacy analysis will be carried out using an analysis of covariance (ANCOVA) method where the change in ADAS-cog14 scores from baseline to Week 26 (Visit 4) will be the outcome variable and treatment group will be main effects. The ADAS-cog14 scores at baseline and ApoE4 will be included as covariates. Baseline will be the last non-missing observation at Visit 2 or before. The standard error of the change from baseline will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

The pattern mixture model methodology will be implemented using SAS procedures MI and MIANALYZE. Specifically, the following steps will be followed:

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data for patients who discontinue early will be multiply imputed as follows:
    - If the patient discontinues due to an AE (Pattern 2) or LOTE (Pattern 3), then missing data will be assumed to follow a distribution similar to the baseline values observed in the placebo arm of the study;
    - If the patient discontinues due to reasons other than an AE or LOTE (Pattern 4), at each time point, missing data will be assumed to follow a distribution similar to scores for patients that are still in the study and randomized to the same treatment group.
- Results of the ANCOVA on the multiply imputed data will be summarized using the SAS procedure MIANALYZE.

19.1.2. Example of steps

Impute any missing data as follows:

Step 1 – Change data structure from ADaM dataset to have one row per subject

Step 2 - Impute Pattern 1 for intermittent missing data (MAR) using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure.

If the imputed values exceed the maximum AVAL (across all subjects/treatments) then reassign the imputed value as this maximum.

Step 3 – Impute Pattern 2 and 3 for missing data due to AE or Lack of Therapeutic Effect (LOTE).

Obtain the mean (1dp) and standard deviation (2dp) across all the patients in the PLACEBO group at baseline and draw at random from the above ditribution to impute missing values.

Step 4 - Impute Pattern 4 for missing data due to reasons other than AE or LOTE.

Do this by visit, each time only include only those that are not missing at that visit or are missing and did not discontinue due to AE or LOTE.

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Step 5 – Combine the datasets back together and re-structure back as per ADaM

Step 6 – Perform the ANCOVA on each imputed dataset using proc GLM. Perform a separate ANCOVA for each post baseline visit (Week 26).

Check the log to ensure that there are no convergence problems across all 100 analyses. If so then use different covariance structures in the following order until this is achieved: type=toep, type=ar(1), type=cs, type=vc

Step 7 – Combine the ANCOVA results using Proc MIANALYZE for each post baseline visit (Week 26).

19.1.3. Corresponding SAS code

```
*** SAS code example ***;

Step 2 SAS code:
proc mi data=DATAIN nimpute=100 seed=545269733 out=MONOTONIC;
var TRTPN BASE Visit_3 Visit_4;
mcmc chain=multiple impute=monotone;
run;

Step 3 SAS code:
data MONOPAT23 ;
set MONOPAT23 ;
impute = &mean. +(&sd.*rannor(545269733)) ;
run ;

where &mean. = mean for PLACEBO and &sd. = standard deviation for
PLACEBO.

Step 4 SAS code:
proc mi data=DATA1 out=WEEK_X seed=545269733 nimpute=1 ;
by _Imputation_;
var TRTPN BASE Visit_3 - Visit_X ;
monotone regression;
run;

Step 6 SAS code:
ods listing close;
ods output  LSMeans=LSOUT_X    Estimates=DIFFOUT_X ;
proc glm data=ANCOVADAT (where = (AVISITN=X)) ;
by _Imputation_  ;
class TRTPN APOE4C ;
model chg = TRTPN BASE APOE4C  / solution ;
lsmeans TRTPN / stderr pdiff=control cl ;
estimate ' Piromelatine - Placebo'  trtpn -1 1 ;
run ;

Step 7 SAS code:
**COMBINE LSMEANS;
ods output ParameterEstimates=LSOUT_X_FINAL ;
proc mianalyze data=LSOUT_X;
```

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```
 by TRTPN ;
 modeleffects LSMEAN  ;
 stderr STDERR ;
run ;

**COMBINE DIFFS;
ods output ParameterEstimates=DIFFOUT_X_FINAL ;
proc mianalyze data=DIFFOUT_X;
 by PARAMETER ;
 modeleffects ESTIMATE ;
 stderr STDERR ;
run ;
```

Please note, this is only example, programming can be updating according to analysis requirements.

19.2. Appendix 2. ANCOVA without imputation for missing data

19.2.1. Extract from SAP

Efficacy analysis will be also carried out using an ANCOVA method where the CGIC Week 13 (Visit 3) and Week 26 (Visit 4) will be the outcome variable and treatment group will be main effects. The CGIC score at baseline and ApoE4 will be included as covariates. The standard error will also be included. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

19.2.2. Corresponding SAS code

```
*** SAS code example ***;

*** IF THERE IS NO IMPUTATION, RUN NORMAL ANCOVA IN PROC GLM FOR THE
GIVEN AVISITN:

ods listing close;
ods output
     LSMeans=LSOUT_X
     Estimates=DIFFOUT_X
  LSMeanCL=LSOUTCI_X
  LSMeanDiffCL=DIFFOUTCI_X
  modelanova=PVAL_X (where=(HypothesisType=3));
proc glm data=ADEFF (WHERE=(AVISITN=X)) ;
 class TRTPN  ;
 model CHG = TRTPN APOE4N BASE / solution ;
 lsmeans TRTPN / stderr pdiff=control cl ;
 estimate 'Piromelatine - Placebo'  trtpn -1 1 ;
run ;
```

Please note, this is only example, programming can be updating according to analysis requirements.

19.3. Appendix 3. MMRM model

19.3.1. Extract from SAP

Change in ADAS-cog14 scores from baseline over Week 26 (Visit 4) will be also analyzed using a MMRM model utilizing all baseline and postbaseline data during double blind period to assess any differences in treatment effects over time. The model will include fixed effects of treatment, visit, and treatment by visit interaction, with baseline score and ApoE4 as covariates. The global treatment effect estimates will be reported, with 95% confidence intervals and *P* values. Baseline will be the last non-missing observation at Visit 2 or before. The adjusted mean difference between treatments versus placebo will be presented along with the standard error and a 95% confidence interval.

These analyses will be performed using PROC MIXED in SAS, and adjusted means will be obtained by using the LSMEANS statement.

19.3.2. Corresponding SAS code

```
*** SAS code example ***;

MMRM USING PROC MIXED:
ods output Diffs=DIFFOUT LSMeans=LSOUT tests3=EFFECTOUT ;
proc mixed data=DATIN (where= (CHG ne .)) ;
 class TRTPN AVISITN APO4EC SUBJID ;
 model CHG = TRTPN AVISITN TRTPN*AVISITN BASE APOE4C / ddfm=kr
solution ;
 repeated AVISITN / subject=SUBJID type=un ;
lsmeans TRTPN*AVISITN / cl diff=control('1' '&AVISITN.) ;
run ;

Please note, this is only example, programming can be updating according to analysis
requirements.
```

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