A Randomized Pivotal Study of Renew™ NCP-5 for the Treatment of Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type (Version Number 3.1)

Statistical Analysis Plan
Version 1.1

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Prepared by:
Navitas Clinical Research, Inc.
11300 Rockville Pike, Suite 500
Rockville, MD 20852

Senior Statistician Signature: _____ Date: 03 Dec 2020

Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

Sponsor Signature: _____ Date: _____

12/3/2020

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List of Abbreviations

Abbreviation	Definition
AA	Alzheimer's Association
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive
ADCS-ADL	Alzheimer's Disease Co-op Study-Activities and Daily Living
ADCS-CGIC	Alzheimer's Disease Co-op Study-Clinical Global Impression of Change
AE	Adverse Event
AI	Artificial Intelligence
APOE	Apolipoprotein E
BMI	Body mass index
CBC	Complete blood count
CBF	Cerebral blood flow
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
CVR	Cerebrovascular reactivity
eCRF	Electronic case report form
ECG	Electrocardiogram
HDL-C	High density lipoprotein cholesterol
ICH	International Council on Harmonisation
LDL-C	Low density lipoprotein cholesterol
LM	Logical Memory
LMII	Logical Memory Sub-Scale II of the Wechsler Memory test
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
ML	Machine Learning
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NIA	National Institute on Aging
NPI	Neuropsychiatric Inventory
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical analysis software
SD	Standard deviation
TEAE	Treatment emergent adverse events
TUG	Timed Up & Go
UADE	Unanticipated adverse device effect

UAE	Unanticipated adverse effect
vADAS-Cog	Vascular Dementia Assessment Scale Cognitive Subscale
WHODRUG	WHO Drug Dictionary
COVID-19	Coronavirus Disease 2019

1. Introduction

This Statistical Analysis Plan (SAP) describes planned statistical analysis (except for primary analysis, some secondary and exploratory endpoint analysis) and reporting for Renew Research, LLC's study Renew™ NCP-5-1001 entitled "A RANDOMIZED PIVOTAL STUDY OF RENEW™ NCP-5 FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE OR MILD DEMENTIA OF THE ALZHEIMER'S TYPE".

This SAP is developed based on International Council on Harmonisation (ICH) E3 and E9, and with references to the following document:

- Protocol: 16 April 2020 Version Number v3.1

This SAP will be used as a work description and guidelines for the focus of the activities and analyses to be performed by the NCR statistician involved in this clinical trial. All analyses (except primary analysis, two secondary endpoints namely Alzheimer's Disease Cooperative Study-Activities and Daily Living (ADCS-ADL) and Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog14) analyses, as well as exploratory endpoints measured with magnetic resonance imaging (MRI) and deep tissue oxygenation via near infrared spectroscopy, which are addressed in a separate statistical analysis plan) will be performed by the NCR statistician. Consequently, none of the investigators involved in the study will perform any of the statistical analyses themselves.

1.1 Coronavirus Disease 2019 (COVID-19)

The COVID-19 pandemic outbreak occurred midway through enrollment and treatment for this study. This SAP will describe analyses to be performed to assess the impact of COVID-19 on the study and methods for handling missing data due to the effects of COVID-19 on study subjects and sites.

The NCR statistical analyses will be carried out using statistical analysis software (SAS) version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

2. Objectives

2.1 Primary Objective:

The primary objective of this study is to determine the efficacy of Renew™ NCP-5 treatment for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or Mild Dementia of the Alzheimer's type as measured by changes in cognition.

2.2 Secondary Objectives:

The secondary objectives of this study are to:

- Evaluate the safety of Renew™ NCP-5 therapy in treatment for MCI due to AD and mild dementia of the Alzheimer's type.
- Confirm the effectiveness of Renew™ NCP-5 treatment through additional neuropsychological testing.

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Evaluate the physiological mechanism of action of Renew™ NCP-5 treatment related to cognition as measured by cognitive and neuro-behavioral assessments, biological markers, ultrasound, and laboratory assessments.
- Understand the relationship of hippocampal volume change over time to changes in cognition.
- Compare ADAS-Cog12 scores at 12, 24, 36, and 48 weeks between an external control arm of digital twins and each of the actual treatment and active sham groups.

3. Investigational Plan

3.1 Overall Study Design and Plan

This is a single-blind, parallel design, and multi-site study. Subjects will be prospectively randomized to treatment or active sham (in a 1:1 ratio) using stratification of cognitive decline (MCI due to AD vs. mild AD) and Cerebrovascular Reactivity (CVR) score (low/medium vs. high/very high) at multiple sites. Randomization assignments will be made using permuted blocks. Investigators shall receive the assignments from an Interactive Web Response System (IWRS).

Prior to randomization, subjects will be diagnosed with either Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type, based on the study checklist developed, which follows the 2011 National Institute on Aging (NIA)-Alzheimer's Association (AA) "core clinical criteria" guidelines. After the subject completes the Mini Mental State Examination 2 (MMSE2), the Logical Memory Sub-Scale II of the Wechsler Memory test (LMII), and the Montreal Cognitive Assessment (MOCA), the investigator will review the results and complete the 2011 NIA-AA study checklist which identifies the "core clinical criteria" for diagnosis of probable AD dementia as indicated by the presence of cognitive and/or behavioral symptoms. Positive responses to the first five questions are required for inclusion in the mild AD cohort. If the responses to the first five questions within the checklist for the diagnosis of probable AD dementia are not positive, the investigator will then complete the 2011 NIA-AA "core clinical criteria"

study checklist for MCI due to AD. Responses to the first four questions of that study checklist for the diagnosis of MCI due to AD must be positive, and the clinical impression must conform with typical presentation of individuals for whom there is an intermediate level of certainty that they have MCI due to AD, in order for subjects to be included in the MCI due to AD cohort.

The MOCA, Logical Memory (LM), MMSE2, and the complaint of memory loss by the subject and/or caregiver will be used to assess the subject; however, eligibility for the study will be determined by a MOCA score of greater than or equal to 11. The efficacy of Renew™ NCP-5 treatments to influence cognitive symptoms will be evaluated through performance on the Vascular Dementia Assessment Scale Cognitive Subscale (vADAS-Cog) compared to the active sham treatment group.

Subjects, ages 55-85, will be consented for 13 months study participation, and will receive thirty-five 60-minute Renew™ NCP-5 treatment sessions during a 7-to-12-week initial treatment period, and then transition to a lower frequency maintenance period (twice a week) for a total treatment period of 24 weeks. During the initial treatment period (~1-12 weeks) subjects should be treated five days per week but at a minimum receive treatments three days per week. For subjects who are unable to complete 5 treatment days per week, the treatments should be spread-out as much as possible. In order to complete 5 treatments per week, it is permissible for those subjects to have 2 treatments per day as long as there are no more than 3 days between treatments. If two treatments are conducted on the same day, subjects will need to wait a minimum of one-hour between treatments. Treatments should be completed per the above schedule. The schedule may be adjusted due to holidays or extenuating circumstances. If subjects need to miss visits during any particular week, then treatments should be added to the week prior to or after the missed visits. A total of 35 treatments must be completed within the 12-week period. More than 7 days between treatments would be considered a protocol violation.

Once the first 35 treatments have been administered, subjects will start the maintenance period. During the maintenance period, subjects should be treated two days per week, one session per day with a minimum of two full days between each treatment. Subjects may be rescheduled on an as needed basis as long as 6 treatments are maintained within a 3-week period. Rescheduling should be kept to a minimum and all efforts should be made to have treatments every week.

Assessment visits should occur the day following the last treatment session but no later than 2 days (48 hours) after the last treatment.

If necessary, on an as-needed basis, a treatment session of 30 minutes or more (≥ 30 minutes) will be considered as a completed session.

The investigator will assess vADAS-Cog at baseline, 6, 12, 18, 24 weeks, 9 month and 12 months, or upon termination of treatment. Testing sessions will include additional secondary psychological assessments including the National Institute on Aging's Alzheimer's Disease Cooperative Study-Clinical Global Impression Scale (ADCS-CGIC) by the clinician and patient/caregiver and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Trail Making Test B, and ADAS-Cog. The ADCS-ADL, ADCS-CGIC, Logical Memory and Trail Making will be completed by blinded psychometricians.

Subjects will receive Magnetic Resonance Imaging (MRI) brain scans at screening to ensure there is no existing exclusionary brain pathology. Brain pathology would include evidence of infection, infarction (including multiple lacunas in a critical memory structure), or other focal lesions. Central Reading of the MRIs will be conducted at Massachusetts General Hospital (MGH). Subjects who are re-screened for this study may utilize their initial screening MRI scan to determine eligibility if the initial screening MRI was completed within 90 days of re-screening. At 24 weeks and end of study (12 month), an MRI will assess changes in hippocampal volume, a biologic marker for AD. A repeat scan may be obtained if necessary. Additionally, as exploratory endpoints, subjects treated at selected sites will receive Transcranial Doppler or the Moor deep tissue oxygenation to evaluate cerebral blood flow at study start and periodically throughout the trial period.

Safety evaluation, including ongoing review of adverse events and vital signs will occur at every visit throughout the study. This trial will have frequent interim analyses to stop accrual early for expected success or for futility as outlined in more detail below.

For exploratory endpoints, blood samples will be drawn at screening, 12 weeks, 24 weeks and 12 months, or upon termination of treatment. A repeat lab draw may be obtained at any time if needed. Polymorphism of the apolipoprotein E (ApoE) gene and its effect on modulating hippocampal change will be assessed at baseline. Additional exploratory lab endpoints include assessment of blood viscosity, inflammatory markers, and blood fibrinogen at baseline, 12 weeks, 24 weeks and 12 months, or upon termination of treatment. Exploratory endpoints of balance, functional mobility, and fall-risk will be measured via the Timed Up & Go (TUG) test and the Functional Reach Test baseline, weeks 6, 12, 18, 24, 9 month and 12 months, or upon termination of treatment. Neuro-behavioral symptoms will be assessed using the Neuropsychiatric Inventory (NPI) at baseline, weeks 6, 12, 18, 24, 9 month and 12 months, or upon termination of treatment.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint for this study is the average of the change from baseline in vADAS-Cog score at 12, 18 and 24 weeks after initiation of treatment. vADAS-Cog is an expanded version of the ADAS-Cog

assessment, and the former has been shown to be a more sensitive measure of cognition than ADAS-Cog in subjects with vascular burden in the brain.

The vADAS-Cog represents a collection of tests of different domains of brain function.

A 2-point average change from baseline in vADAS-Cog at 12, 18 and 24 weeks after initiation of treatment will be used to determine effectiveness. Examples of the typical functional changes associated with a 2-point change in vADAS-Cog include:

- Improvement in orientation – Subject can now remember current date and day of week;
- Less errors in naming - 50% reduction in mistakes naming a real object;
- Improvement in following commands – subjects failing to follow 1/5 simple commands instead of 3/5 commands previously failed;
- Improvements in spoken language - misunderstanding decreases from moderately severe to mild (3-5 errors mean mild);
- Better constructional praxis - 40% improvement in number of figures copied correctly;
- Better word recall - 20% improvement in ability to remember words immediately after hearing them 3 times;

It is expected that the effect of the treatment will be demonstrated first at 12 weeks but will maintain or improve through to 24 weeks. Accordingly, since the 12 week (the completion of initial phase of treatment), 18 week and 24 week (end of maintenance phase) vADAS-Cog scores represent the entire expected period of the treatment duration, it is appropriate to measure the average of 12, 18 and 24 week vADAS-Cog scores as the primary endpoint for this study.

3.2.2 Secondary Safety and Effectiveness Endpoints

Because there is no gold standard to measure the changes from treatment in cognition for MCI or mild AD, secondary endpoints will include assessments performed in other similar studies. While cognitive and imaging assessments may show changes over time, it is important to assess the importance of change to the clinician and caregiver (ADCS-CGIC) and the ability of the subject to carry out activities of daily living (ADCS-ADL). The Trail Making Test B is used in many studies to assess executive function, a key to continued functioning for the patient. Because the vADAS-Cog includes the ADAS-Cog14 that has been used to assess changes in cognition in pharmaceutical studies, it is important to compare it to the findings from the vADAS-Cog.

Secondary effectiveness endpoints of the study include:

- The safety of Renew™ NCP-5 treatments as reflected in adverse events, labs and vital signs;

- The average of the change from baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Total Score at 12, 18 and 24 weeks after initiation of treatment;
- The answers to the National Institute on Aging's Disease Cooperative Study-Clinical Global Impression of Change Scale (ADCS-CGIC) at 12, 18 and 24 weeks after initiation of treatment;
- The average of the change from baseline in executive function, assessed by the Trail Making Test B at 12, 18 and 24 weeks after initiation of treatment;
- The average of the change from baseline in ADAS-Cog14 at 12, 18 and 24 weeks after initiation of treatment. ADAS-Cog14 score will be calculated using the subtests from the vADAS-Cog test and will not be conducted as a separate test.

3.2.3 Payor-based Endpoints

The payor-based endpoints, described below, will be used to assess the clinical and cost effectiveness of the Renew™ NCP-5 external counter-pulsation (ECP) for patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type. Effectiveness of ECP on cognitive impairment, compared to active sham group, measured by the clinical effectiveness endpoints identified, will be key in communicating the value and benefits of adding ECP as a treatment option for this patient population. In order for physicians to widely access ECP as a treatment option for their patients, reimbursement from commercial payers will be required. To facilitate reimbursement, the study is measuring the impact of ECP on health related quality of life (HRQoL), reduction in disease burden,and health resource use (HRU) to help assess the cost effectiveness of ECP, and potential cost savings for health systems and payers. Results from this study will be presented to Centers for Medicare and Medicaid Services (CMS) and commercial insurers to initiate reimbursement approval of ECP.

- **Health Resource Utilization (HRU) data**: For detailed endpoint of HRU, please see **Appendix C.**

- **vADAS Cog Scores**: the difference in change from baseline at 24 weeks, 9 months, and 12 months after initiation of treatment, and an average of 24 weeks, 9 months, and 12 months

- **ADCS-ADL Scores**: the difference in change from baseline at 24 weeks, 9 months, and 12 months after initiation of treatment, and an average of 24 weeks, 9 months, and 12 months

- **Fall Risk Assessment/Functional Reach Test/TUG Test Scores**: the difference in change from baseline at 24 weeks, 9 months, and 12 months after initiation of treatment, and an average of 24 weeks, 9 months, and 12 months

- **NPI Aggression Index Scores**: the difference in change from baseline at 24 weeks, 9 months, and 12 months after initiation of treatment, and an average of 24 weeks, 9 months, and 12 months

- **QOL/Patient Survey**: the answers to the QOL/patient survey at 12 months after initiation of treatment

3.2.4 Exploratory Endpoints

Imaging studies may be important in understanding the mechanism by which treatment results in change in cognition or delays the progression of the disease. Understanding that there is a vascular component to MCI and mild AD, assessing changes in cerebral blood flow can inform the mechanism of change. Research indicates that hippocampal volume change over time, measured by MRI, has potential as a marker for MCI and AD. MRI will be conducted at screening after all other assessments have found the subject to be eligible to participate in the study. This will allow results confirming no brain pathology, which would include evidence of infection, infarction (including multiple lacunas in a critical memory structure), or other focal lesions to be available for review at the baseline visit. If a history of cerebral aneurysm is suspected, the subject will be referred to their primary physician and/or neurologist.

The exploratory endpoints for this study include:

- Evidence of altered peripheral or cerebrovascular physiology including:
  - The observed value and change from baseline in hippocampal volume measured by MRI at 24 weeks and 12 months after initiation of treatment
  - Changes from baseline to 24 weeks after initiation of treatment or active sham in:
    - Cerebral blood flow (CBF) in multiple regions (hippocampus, precuneus, parietal, inferior frontal lobe) measured by arterial spin labeling between the treatment and active sham groups from screening, to 24 weeks and 12 months (selected sites only);
    - Global cerebral blood flow as measured via MRI
    - White matter hyperintensities as measured via MRI
    - CBF velocity in cerebral arteries as measured by Transcranial Doppler at baseline, 12 and 24 weeks (selected sites only)
    - Endothelial function via flow-mediated dilation (FMD) (brachial or femoral), as measured by ultrasound at baseline, 12 and 24 weeks (selected sites only)
    - Arterial stiffness via pulse wave velocity (PWV) measured by arterial tomography or ultrasound at baseline, 12 and 24 weeks (selected sites only)

- Arterial stiffness via augmentation index measured by arterial tomography at baseline, 12 and 24 weeks
- Deep tissue oxygenation (hemoglobin concentration and SO2) via near infrared spectroscopy at baseline, 12 and 24 weeks
- Blood viscosity at baseline, 12 and 24 weeks (selected sites only)
- Lipid panel: total cholesterol, LDL-C, HDL-C, triglycerides, Blood fibrinogen at baseline, 12 and 24 weeks
- Inflammatory markers: C-Reactive Protein (CRP), Lp-PLA2 and MPOS at baseline, 12 and 24 weeks
- CBC: including Red Cell Distribution Width (RDW) & Hemoglobin at baseline, 12 and 24 weeks

- Difference in change from baseline at 12 and 24 weeks in the Behavioral Assessment measured via NPI Agitation/Aggression
- Difference in change from baseline at 12 and 24 weeks in balance, functional mobility, and fall-risk assessment measured via Timed Up & Go (TUG) test and the Functional Reach Test
- Time course comparative analysis between treatment and active sham groups in ADAS Delayed Word Recall (a sub-test of the vADAS cog) at baseline, 12 and 24 weeks
- Time course comparative analysis between treatment and active sham groups in ADAS Word Recognition (a sub-test of the vADAS cog) at baseline, 12 and 24 weeks
- In an exploratory analysis, ADAS-Cog12 scores at 12 weeks, 24 weeks, 9 months, and 12 months will be compared between an external control arm of digital twins and each of the actual treatment and active sham groups. An external control arm of digital twins will be used to estimate the change in ADAS-Cog12 total score for control subjects matched to each treatment and active sham groups. Digital twins are generated from a statistical model of disease progression with the same baseline characteristics as actual study participants. The observed values of the change from baseline ADAS-Cog12 total scores for the treatment and active sham groups will be summarized in terms of descriptive statistics (number of subjects, mean, and standard deviation) and compared to the predicted values for each group from the external control arm and for each time point above a paired difference test will be used to estimate the effect of the treatment and active sham over controls.
- Proportion of patients with vADAS responder at post-treatment visits. The responder is defined as the vADAS change from baseline score <= -2 and below.

3.3 Randomization

Subjects will be prospectively randomized to treatment or active sham (in a 1:1 ratio) using stratification for Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type, and CVR

score at multiple sites. Subjects will be assessed for stratification and then randomized within strata to either the treatment group or active sham group with one treated subject for one active sham subject. Randomization assignments will be made using permuted blocks. Investigators shall receive the assignments from an Interactive Web Response System. The following factors will be used for stratification prior to randomization: cognitive decline (MCI due to AD vs. mild AD) and CVR score (low/medium vs. high/very high).

3.4 Sample Size and Power Analyses

These will be discussed in Appendix A1, primary statistical analysis plan, which is a separate document **prepared by Berry Consultants as an adaptive design.**

3.5 Blinding and Unblinding

For this study, the subject and the psychometrician/designee will be blinded. Neither the Renew™ NCP-5 operator nor the PI will be blinded. The psychometrician/designee administering all cognitive tests should be blinded. There does not seem to be any reason that the subject or psychometrician will be unblinded in the event of a serious adverse event. Only the investigator, who is unblinded, will need to assess what intervention the subject may need or whether the subject can continue in the study.

4. General Statistical Considerations

All data collected will be presented in listings. Subjects will be identified in the listings by the subject identification number concatenated with the site number.

Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

Data from subjects receiving active sham will be pooled across cohorts for all presentations.

Unless otherwise specified, the following treatment groups will be used for summary purposes:

- Renew™ NCP-5
- Active sham
- Overall (optional)

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum).

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, and confidence intervals (CIs) will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. p-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999."

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

For the change from Baseline safety summaries, Baseline will be defined as the last non-missing measurement (including repeated and unscheduled assessments) before the treatment.

4.1 Missing Data due to COVID-19

In general, the estimand for this study will use the Treatment Policy Strategy for intercurrent events, as planned during the design of this study. However, the COVID-19 pandemic was not anticipated, and the methodology will be changed for some intercurrent events. To make the analysis results applicable to the post-pandemic situation in which the virus is present in society but strict shelter-in-place orders and lack of personal protective equipment do not preclude routine office visits, subjects missing primary, secondary, or exploratory endpoint data due to the pandemic but not due to (actual or suspected) COVID-19 infection will have missing or out-of-window data addressed using the Hypothetical Strategy for intercurrent events. Under this strategy, partial data will be used for more efficient estimates of the analysis parameters.

The protocol deviation log, COVID-19 and disposition eCRFs will record reasons for missed visits, interruptions in study treatment, and reasons for treatment discontinuation, including COVID-19 disruption. For reasons related to COVID-19, the study team will review before database lock and unblinding and assign a category for missing data, or data present after COVID-19 interruption, as defined below:

- Not COVID-19 related, site closure: subject discontinues treatment or discontinues the study for reasons not related to the pandemic, but the site was later closed due to COVID-19 during the time frame at which the subject's primary or secondary endpoint data would have been collected, had the subject been in the study.

- COVID-19 infection: subject is missing results during timepoint of interest due to confirmed or suspected COVID-19 infection prior to this period.
- COVID-19 related, missing: subject is missing results during timepoint of interest after discontinuing treatment and/or study due to COVID-19 and did not have confirmed/suspected infection (e.g. stay at home order, site closure, concerns about immunosuppressant use, etc.)
- COVID-19 related, non-missing: subject has results during timepoint of interest, but discontinued treatment prior to timepoint due to COVID-19, has a delay in the timing of an assessment > 14 days to timepoint due date, or has a gap in treatment of > 14 days prior to timepoint due to COVID-19.

4.2 Subgroups

Subgroup analyses will be repeated for the secondary and select exploratory analyses for the following subgroups:

- Cognitive decline (MCI due to AD vs. mild AD)
- CVR score (low/medium vs. high/very high)

4.3 ECP Treatment Quality

ECP treatment quality will be used as a cofactor in various exploratory analyses. ECP treatment quality is an indicator of the level of "fine-tuning" of the ECP treatment session in terms of the compression PSI level and the compression timing. ECP treatment session quality depends on the specific cardiovascular characteristics of the subject (blood pressure waveform) and the subject's tolerance for the device's compression pressure (maximum PSI). The quality of the blood pressure waveform is measured by the ratio (IP/PS) of the height of the point at which the enhanced diastolic wave separates from the systolic wave (inflection point or IP) in relation to the systolic peak height (peak systolic or PS). ECP treatment quality is a pass/fail measure of the quality of the complete regimen of ECP sessions for a single subject based on criteria that must all pass.

- Criteria 1: exclude treatment group subjects if the average of the ECP session maximum PSI values across all sessions is less than 3.5 PSI. Also exclude active sham group subjects if the ECP session maximum PSI values across all sessions is 0.7 PSI or greater.
- Criteria 2: exclude treatment group subjects if IP/PS is less than 0.3 or greater than 0.8.

5. Analysis Populations

The analysis population in this SAP includes intent-to-treat (ITT), per-protocol (PP), and safety population as described below.

The **ITT population** includes all subjects who are enrolled and randomized into either active treatment group or active sham group. The randomized group assigned to the subjects will be used for the ITT population. Out-of-window assessments caused by COVID-19 pandemic restrictions will remain aligned with the originally intended visit (i.e, an out-of-window 18 week visit is listed as an 18 week visit). A sensitivity analysis without these out-of-window visits affected by COVID 19 will be conducted separately.

The **PP population** includes all ITT population subjects with the following exceptions and modifications. The PP population will be used for sensitivity analyses.

- Rule 1 (for assessment compliance): Exclude subjects who are missing the week 24 VADAScog assessment.
- Rule 2 (for treatment compliance): Exclude subjects with less than a total of 20 weeks of treatment with at least one treatment per week.
- Rule 3 (for treatment compliance): The actual treatment (Renew™ NCP-5 or active sham) that patients received will be used for PP population.
- Rule 4 (for COVID-19 pandemic disruptions): Out-of-window assessments caused by COVID-19 pandemic restrictions will remain aligned with the originally intended visit (i.e, an out-of-window 18 week visit is listed as an 18 week visit). A sensitivity analysis without these out-of-window visits affected by COVID 19 will be conducted separately. Use Rule 4 first, and then apply Rules 1, 2 and 3.

The **safety population** includes all randomized subjects who received either active treatment or active sham treatment. The actual treatment that patients received will be used for the safety population. Safety population is used in all secondary (except ADCS-ADL and ADAS-Cog14) and exploratory analyses.

6. Disposition

The completion of the study is defined as the time when the randomized subjects finish all treatments and complete study assessments at 6, 12, 18, 24 weeks, 9 month, and 12 months/end of study assessments. The number of subjects randomized, completed the study, and discontinued from the study, as well as the reasons discontinuation from the study occurred for each subject will be summarized. The number of subjects who discontinue treatment or study due to COVID-19 will be summarized with this as the reason for discontinuation. The disposition data will be presented in a listing.

7. Demographics and Baseline Characteristics

Demographics will be summarized for Intent-to-Treat population by treatment group as defined in Section 4. For continuous data (age, height, weight, and body mass index [BMI]), number of subjects, mean, median, SD, minimum, and maximum will be summarized. For categorical data (sex, race, ethnicity, educational level, etc.), frequency count and percentages will be summarized.

Demographics, baseline characteristics, and medical history data will be presented in listings.

8. Prior and Concomitant Medications/Procedures

Prior medication is defined as any medication taken before the treatment. Concomitant medication is defined as any medications taken after the treatment up to the end of the study. Prior and concomitant medications will be coded using WHO Drug Dictionary (WHODRUG, version WHO-DD B3/C3) and summarized by medication category and coded term, and treatment group as defined in Section 4 above.

Prior and concomitant medications/procedures will be presented in listings.

9. Safety Analyses

Safety will be monitored throughout the trial as follows: monitoring and recording of anticipated adverse effects, unanticipated adverse effects (UAEs), serious adverse effects, unanticipated adverse device effects (UADEs), the assessment of laboratory parameters, 12-lead electrocardiogram, and vital sign measurements. Safety population will be used for all safety analyses.

9.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA (version 22). Treatment emergent adverse events (TEAE) are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment. TEAEs will be summarized by system organ class, preferred term, severity (mild, moderate, and severe), relationship to study treatment (not related, suspected, and probably related), and treatment group as defined in Section 4. COVID-19 Infection TEAEs will be summarized by system organ class, preferred term, severity (mild, moderate, and severe), and treatment group as defined in Section 4. Serious AEs (SAE) and AEs leading to death will also be summarized. All AEs will be presented in a listing.

9.2 Clinical Laboratory Evaluation

The laboratory evaluations that will be performed are listed below.

- **Comprehensive Metabolic Panel (CMP) –** Blood test to assess levels of electrolytes, how well the kidneys and liver are working, and blood glucose. Includes 14 blood tests that provide information about the current health status of the patient. Performed at baseline to assess whether the subject is healthy enough to participate in the study. Performed at intervals during the study to confirm no change in subject's health. Vitamin B12 and TSH will also be assessed.
- **ApoE –** Polymorphism of the apolipoprotein (ApoE) gene and its effect in modulating hippocampal change will be assessed.
- **Lipid Panel –** Provide a profile of cholesterol, HDL, LDL, and triglycerides to assess cardiac risk and general health of the subject
- **Complete blood count (CBC) –** Gives information about the cells in a patient's blood, including hemoglobin, hematocrit, and white blood cells to assess patient's general health.
- **C-reactive protein (CRP) and Lp-PLA2 and MPOS –** Blood markers for inflammation in the body. These inflammatory markers are implicated in the pathogenesis of AD and VD. CRP is a strong marker of vascular disease in early stages of the disease.
- **Blood viscosity –** AD patients have significantly increased whole blood viscosity which is correlated with disease severity.

The summary of laboratory test results and change from baseline will be presented in tables by time point and treatment group as defined in Section 4. Abnormal laboratory test results will also be summarized by frequency count and percentage by test parameter, time point, and treatment group as defined in Section 4. All laboratory test results will be presented in listings with abnormal and clinically significant flags marked.

9.3 Vital Signs

The following vital signs assessments are included in the protocol:

- Height- at screening visit only
- Weight
- Body temperature
- Respiratory rate
- Heart rate
- Blood pressure (sitting after 5 minutes on assessment visits, Supine after five minutes on treatment visits).

The summary of vital sign results (except height) and change from baseline will be presented in a table by time point and treatment group as defined in Section 4. All vital sign results will be presented in a listing.

9.4 Physical Examination

Abnormal physical examination findings will be presented in a listing.

9.5 12-Lead Electrocardiogram

Abnormal electrocardiogram (ECG) findings will be presented in a listing.

10. Primary Efficacy Analysis

10.1 Integrated Change From Baseline on VADAScog: 12, 18, 24

Please refer to **Appendix A1 ADR** for detailed information of primary efficacy analysis.

11. Secondary Efficacy Analyses

The only type I error controlled analysis of secondary endpoints is for the ADCS-ADL (Appendix 2). This analysis will be considered significant if the primary analysis is significant and the posterior probability of superiority for Renew™ NCP-5 on the ADCS-ADL analysis is greater than 97.7%. There are no type I error adjustments for the additional secondary efficacy analyses. Each will be summarized using a two-sided 5% type I error rate.

11.1 ADCS-CGIC at 12, 18, and 24 Weeks after Initiation of Treatment

The descriptive summary of frequency count and percentage in ADCS-CGIC results (Marked Improvement, Moderate Improvement, Minimal Improvement, No Change, Minimal Worsening, Moderate Worsening, and Marked Worsening) at 12, 18, and 24 weeks will be provided by treatment group.

For subjects not impacted by COVID-19 with missing ADCS-CGIC results the following imputation approach will be used:

- Completely missing results post-baseline – 'Marked Worsening' imputed as subjects' Response at each post-baseline visit.
- Completely missing result at visit but assessment was attempted at a prior visit – One-worse than the last evaluable Response is imputed, per table below.

Imputation of One-worse than the Last Evaluable Overall Response:

Last Evaluable Response	**Imputed Response**
Marked Improvement	Moderate Improvement
Moderate Improvement	Minimal Improvement
Minimal Improvement	No Change

No Change	Minimal Worsening
Minimal Worsening	Moderate Worsening
Moderate Worsening	Marked Worsening
Marked Worsening	Marked Worsening

For subjects who have been impacted by COVID-19, the following methods will be used in the analysis of overall response at Week 52:

- COVID-19 infection: the imputation method specified above will be used to impute a response

For the analyses of the response at each visit, each category (Marked Improvement, Moderate Improvement, Minimal Improvement, No Change, Minimal Worsening, Moderate Worsening, and Marked Worsening) will be assigned an ordinal score of 1, 2, 3, 4, 5, 6, or 7. A proportional odds logistic model for ordered categorical data with treatment group as the effect and cognitive decline (MCI due to AD vs. mild AD), CVR score (low/medium vs. high/very high), ApoE (positive vs. negative), and ECP treatment quality as cofactors, will be used to compare between treatment groups. The estimate of the common odds ratio comparing between treatment groups will be provided along with the corresponding 95% CI and p-value. In addition, the p-value testing the appropriateness of the proportional odds assumption will be provided.

The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19 (i.e. will not contribute to the numerator or denominator). The subgroup analyses will be performed using the same method with ITT population within each subgroup factor described in section 4.

11.2 The Average of the Change from Baseline in Executive Function, Assessed by the Trail Making Test B at 12, 18, and 24 Weeks after Initiation of Treatment

The observed score at each scheduled time point, change from baseline in executive function at 12, 18, and 24 weeks and the average of the changes from baseline at these time points will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

For subjects not impacted by COVID-19 with missing Trail Making Test B results, the following imputation approach will be used:

- For a patient with no visit data, we make the conservative assumption that these patients did not receive any potentially therapeutic levels of treatment. As such, these patients will be

multiply imputed in the analyses from the active sham control arm longitudinal model, regardless of whether they were randomized to treatment or active sham control.

- For patients with a 6-week measurement observed but none of the subsequent endpoint visits, their final subsequent endpoint values will be multiply imputed from the longitudinal model according to their randomization assignment.
- If a patient has one or two of the visits for the integrated primary endpoint, but not all three, the missing primary endpoint visit is not imputed. Rather, the average among the observed visits will be used as the patient's final subsequent endpoint value.

For subjects who have been impacted by COVID-19, the following methods will be used in the analysis of overall response at Week 52:

- COVID-19 infection: the imputation method specified above will be used to impute the missing data

The average of the change from baseline will be analyzed on ITT population using a mixed model ANCOVA with terms of baseline vADAS-Cog score, the baseline value in executive function, treatment group, cognitive decline (MCI due to AD vs. mild AD), CVR score (low/medium vs. high/very high), ApoE (positive vs. negative), and ECP treatment quality as cofactors.

The unstructured (UN) variance-covariance matrix will be used. In the event that this matrix does not allow for model convergence, the following three variance-covariance matrices will be attempted in order until one converges: heterogeneous Toeplitz, heterogeneous compound symmetry, and Toeplitz. The p-value for all terms in the model will be presented, as well as the overall treatment group least squares (LS) means and associated standard errors (SE), and their difference, SE of the difference, 95% confidence intervals (CI) and p-value. The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19. The subgroup analyses will be performed using the same method with ITT population within each subgroup factor described in section 4.

11.3 The Average Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Total Score at 12, 18 and 24 Weeks after Initiation of Treatment

The secondary efficacy endpoint of ADCS-ADL is addressed in a separate statistical analysis plan **(Appendix A2)**, which will have a Bayesian design.

11.4 The Average Change from Baseline in ADAS-Cog14 at 12, 18 and 24 Weeks after Initiation of Treatment.

The secondary efficacy endpoint of ADAS-Cog14 at 12, 18 and 24 weeks after initiation of treatment is addressed in a separate statistical analysis plan **(Appendix A2**), which will have a Bayesian design.

12. Payor-Based Endpoints

The payor-based endpoints will be analyzed on ITT population using one of the two statistical methods below (unless specified otherwise):

1) For the change from baseline with multiple time points, a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline value for the parameter interest, with terms of baseline vADAS-Cog score, the baseline value of the endpoint (if other than vADAS score), treatment group, time point, interaction of treatment group and time point, cognitive decline (MCI due to AD vs. mild AD), CVR score (low/medium vs. high/very high), ApoE (positive vs. negative), and ECP treatment quality as cofactors. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

2) For the average of the change from baseline, a mixed model ANCOVA will be used with terms of baseline vADAS-Cog score, the baseline value of the endpoint (if other than vADAS score), treatment group, cognitive decline (MCI due to AD vs. mild AD), CVR score (low/medium vs. high/very high), and ApoE (positive vs. negative), and ECP treatment quality as cofactors as cofactors. The average of the change from baseline is obtained from non-missing results time points. For example, if there are two non-missing change from baseline out of three time points, the average of change from baseline is made over two available change from baseline results. There is no imputation for missing data implemented unless specified.

The UN variance-covariance matrix will be used. In the event that this matrix does not allow for model convergence, the following three variance-covariance matrices will be attempted in order until one converges: heterogeneous Toeplitz, heterogeneous compound symmetry, and Toeplitz. The p-value for all terms in the model will be presented, as well as the overall treatment group LS means and associated SE, and their difference, SE of the difference, 95% CIs and p-value. Since there are no conclusions regarding the success of the trial drawn from payor-based analyses, there is no type I error adjustment in exploratory analyses.

12.1 vADAS-Cog Follow-up Scores

The observed and change from baseline in vADAS Cog scores at 24 weeks, 9 months, and 12 months will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 12. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

12.2 ADCS-ADL Follow-up Scores

The observed and change from baseline in ADCS-ADL scores at 24 weeks, 9 months, and 12 months will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 12. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

12.3 Fall Risk Assessment/Functional Reach Test/TUG Test Scores

The observed and change from baseline in Fall Risk Assessment/Functional Reach Test/TUG Test scores at 24 weeks, 9 months, and 12 months will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 12. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

12.4 NPI Aggression Index Scores

The observed and change from baseline in NPI Aggression Index scores at 24 weeks, 9 months, and 12 month will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 12. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

12.5 QOL/Patient Survey

The result of QOL/patient survey will be summarized using descriptive statistics including frequency count and percentage based on the answer to each questionnaire at each visit.

12.6 Health Resource Utilization (HRU) Analysis

For details of the HRU analysis, please see **Appendix C.**

13. Exploratory Analyses

The exploratory endpoints with continuous data will be analyzed using one of the two statistical methods (unless specified otherwise):

1) For continuous data with multiple time points, a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline value for the parameter interest, with terms of baseline vADAS-Cog score, the baseline value of the endpoint (if other than vADAS score), treatment group, time point, interaction of treatment group and time point, cognitive decline (MCI due to AD vs. mild AD), CVR score (low/medium vs. high/very high), ApoE (positive vs. negative), and ECP treatment quality as cofactors. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

2) For the average of the change from baseline, a mixed model ANCOVA will be used with terms of baseline vADAS-Cog score, the baseline value of the endpoint (if other than vADAS score), treatment group, cognitive decline (MCI due to AD vs. mild AD), CVR score (low/medium vs. high/very high), ApoE (positive vs. negative), and ECP treatment quality as cofactors. For the exploratory analysis of the primary endpoint vADAScog using ANCOVA model (section 13.17), the missing data will be handled using the method described in section 11.2. For all other exploratory endpoint analyses, there is no imputation for missing data implemented unless specified.

The UN variance-covariance matrix will be used. In the event that this matrix does not allow for model convergence, the following three variance-covariance matrices will be attempted in order until one converges: heterogeneous Toeplitz, heterogeneous compound symmetry, and Toeplitz. The p-value for all terms in the model will be presented, as well as the overall treatment group LS means and associated SE, and their difference, SE of the difference, 95% CIs and p-value. Since there are no conclusions regarding the success of the trial drawn from exploratory analyses, there is no type I error adjustment in exploratory analyses. The same analyses will be repeated using PP population as sensitivity analyses. In addition, the same analyses will be performed using ITT population with excluding the data from the subjects impacted by COVID-19.

13.1 The Observed Value and Change from Baseline in Hippocampal Volume Measured by MRI at 24 Weeks and 12 Months after Initiation of Treatment

The observed value and change from baseline in hippocampal volume measured by MRI at 24 weeks and 12 months after initiation of treatment will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using

the method 1) described in section 13. In addition, the correlation between change from baseline in hippocampal volume and change from baseline in vADAS-Cog, ADCS-ADL, and ADAS-Cog14, as well as ratings from ADCS-CGIC, will be analyzed.

13.2 Cerebral Blood Flow (CBF) and Change from Baseline

CBF in multiple regions (hippocampus, precuneus, parietal, inferior frontal lobe) measured by arterial spin labeling between the treatment and active sham groups from screening, to 24 weeks and 12 months (selected sites only) will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 13.

13.3 Global Cerebral Blood Flow as Measured via MRI

In selected sites MRI will be used to assess global cerebral blood flow at initial screening, 24 weeks, and 12 months.

The global cerebral blood flow will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum), and will be analyzed using the method 1) described in section 13.

13.4 White Matter Lesion Burden as Measured via MRI

In selected sites MRI will be used to assess white matter lesion burden at initial screening, 24 weeks, and 12 months. White matter lesion burden reflects cerebral hypoperfusion and small vessel disease and is a covariate for vascular disease. White matter lesions are tied to disease progression and decreased cerebral blood flow.

White matter lesion burden will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum), and will be analyzed using the method 1) described in section 13.

13.5 Exploratory Analysis of Change From Baseline on vADAScog at week 12

This analysis is described in Appendix A1 and will be a Bayesian analysis.

13.6 Exploratory Analysis of Change From Baseline on vADAScog at week 24

This analysis is described in Appendix A1 and will be a Bayesian analysis.

13.7 Deep Tissue Oxygenation via Near Infrared Spectroscopy and Blood Viscosity at Baseline, 12 and 24 Weeks

Deep tissue oxygenation (hemoglobin concentration and SO2) via near infrared spectroscopy and blood viscosity (selected sites only) at baseline, 12 and 24 weeks will be summarized using descriptive statistics

(number of subjects, mean, median, SD, minimum, and maximum), and will be analyzed using the method 1) described in section 13.

13.8 Lipid Panel: Total Cholesterol, LDL-C, HDL-C, Triglycerides, Blood Fibrinogen at Baseline, 12 and 24 Weeks

Lipid panel: total cholesterol, LDL-C, HDL-C, triglycerides, blood fibrinogen at baseline, 12 and 24 weeks will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum), and will be analyzed using the method 1) described in section 13.

13.9 Inflammatory Markers: C-Reactive Protein (CRP), Lp-PLA2, and MPOS at Baseline, 12 and 24 Weeks

Inflammatory markers: CRP, Lp-PLA2, and MPOS at baseline, 12 and 24 weeks will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum), and will be analyzed using the method 1) described in section 13.

13.10 CBC: Including Red Cell Distribution Width (RDW) and Hemoglobin at Baseline, 12 and 24 Weeks

CBC: including RDW and hemoglobin at baseline, 12 and 24 weeks will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum), and will be analyzed using the method 1) described in section 13.

13.11 Polymorphism of the Apolipoprotein (ApoE) Gene and its Effect in Modulating Hippocampal Changes

The change from baseline in hippocampal volume measured by MRI at 24 weeks and 12 months after initiation of treatment and its relationship with ApoE (positive vs. negative) will be analyzed using the method 1) described in section 13.

13.12 Behavioral Assessment Measured via Neuropsychiatric Inventory (NPI) Agitation/Aggression: Difference in Change from Baseline at 12 and 24 Weeks

The observed value of behavioral assessment measured via NPI Agitation/Aggression and the change from baseline at 12 and 24 weeks will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 13.

13.13 Balance, Functional Mobility, and Fall-risk Assessment Measured via Time up and go (TUG) Test and the Functional Reach Test: Difference in Change from Baseline at 12 and 24 Weeks

The observed value of balance, functional mobility, and fall-risk assessment measured via TUG test and the Functional Reach Test, and the change from baseline at 12 and 24 weeks the change from baseline at

12 and 24 weeks will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 13.

13.14 ADAS Delayed Word Recall and ADAS Word Recognition (a sub-test of the vADAS cog) at baseline, 12 and 24 Weeks, 9 and 12 Months.

The observed ADAS Delayed Word Recall and ADAS Word Recognition (a sub-test of the vADAS cog) and the change from baseline at 12 and 24 weeks, as well as 9 and 12 months will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 13. The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19. The subgroup analyses will be performed using the same method with ITT population within each subgroup factor described in section 4.

13.15 Comparison of ADAS-Cog12 scores at 12 weeks, 24 weeks, 9 months, and 12 months between an external control arm of digital twins and each of the actual treatment and active sham groups.

An external control arm of digital twins will be used to estimate the change in ADAS-Cog12 total score for control subjects matched to each treatment and active sham groups. Digital twins are generated from a statistical model of disease progression with the same baseline characteristics as actual study participants. The observed values of the change from baseline ADAS-Cog12 total scores for the treatment and active sham groups will be summarized in terms of descriptive statistics (number of subjects, mean, and standard deviation) and compared to the predicted values for each group from the external control arm and for each time point above a paired difference test will be used to estimate the effect of the treatment and active sham over controls. The change from baseline in ADAS-Cog14 at 12 weeks, 24 weeks, 9 months, and 12 months will be analyzed pair-wise between external control arm of digital twins vs. Renew NCP-5, and external control arm of digital twins vs. active sham, using the method 1) described in section 13. The schedule of events is included in the main body of the protocol.

Artificial Intelligence (AI) is making great contributions in the healthcare industry. In 2018, through the de novo pathway, CDRH permitted marketing of two software programs that use AI algorithms: IDx-DR for the detection of greater than a mild level of the eye disease diabetic retinopathy in adults who have diabetes, and the Viz.AI Contact application for analyzing computed tomography (CT) results that may

notify providers of a potential stroke in their patients*[1]. These AI-based devices are examples of *discriminative models* trained to detect medical conditions based on imaging data.

Unlearn's goal is to use AI to benefit patients and improve healthcare. Unlearn seeks to continue to expand the frontier of ML (Machine Learning) by utilizing *generative models* in the device and drug development process. Generative modeling of clinical data involves randomly generating subject profiles with the same statistical properties as actual subject records. Unlearn uses a type of generative ML-model known as a Conditional Restricted Boltzmann Machine (CRBM) that can forecast the trajectory of each subject's entire profile as a time-dependent probability distribution associated with subjects' characteristics [1,2]. Sampling from such distributions can be used to impute missing observations, forecast a subject's future state, target alternative combinations of endpoints, or select subgroups of subjects for analysis.

Unlearn's technology can generate digital control subject data that are statistically indistinguishable from actual concurrent controls. Unlearn's technology is built using CRBMs, a type of probabilistic neural network capable of modeling subject-level longitudinal clinical data. A CRBM can be used to generate clinical data forecasting disease progression that have the exact same baseline characteristics as actual subjects enrolled in a study. We call these generated subjects *digital twins*, as they act as digital subjects that simulate patients' outcomes as if they were in a control group. That is, each digital twin provides a per-subject counterfactual. Digital twins reduce variability because of differences in the baseline characteristics of the control and treatment groups, enabling paired statistical analyses.

A Restricted Boltzmann Machine (RBM) is a probabilistic neural network in the form of a latent-variable statistical model described by the probability distribution:

$$p(v) = \int dh\, Z^{-1} \exp\left[\sum_j a_j(v_j) + \sum_\mu b_\mu(h_\mu) + \sum_{j,\mu} W_{j\mu} \frac{v_j}{\sigma_j^2}\frac{h_\mu}{\varepsilon_\mu^2}\right]$$

where Z is a normalization constant ensuring the total probability is 1, a and b are functions characterizing the data type of each data covariate v_j or latent variable h_μ, and W, σ, and ε are parameters. A CRBM adapts this probabilistic neural network to model longitudinal data as a Markov process with observations in regular time intervals. The model for AD used in the Renew NCP-5 s study uses a 3-month cadence in longitudinal observations and makes predictions based on data from the 3-month prior visit.

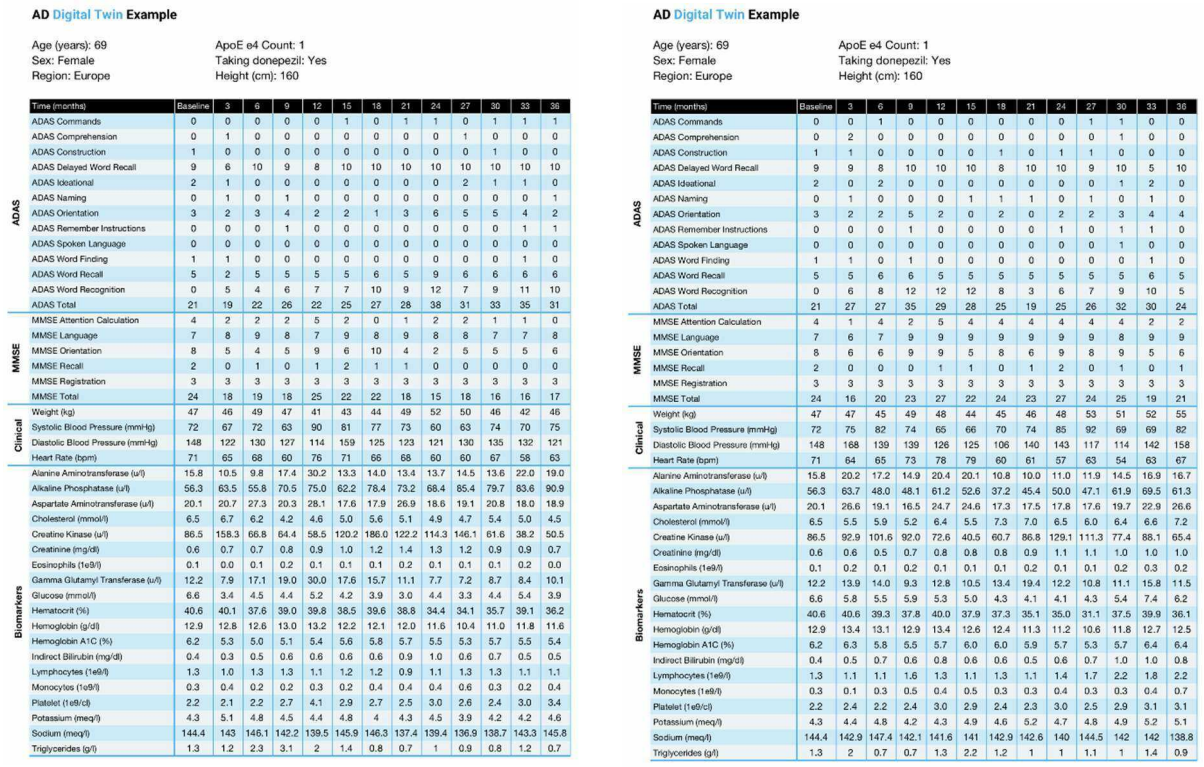
[1]* *See* DEN180001 (granted 4/11/18) *and* DEN170073 (granted 2/13/18).

The model was trained on control arm data from 18 drug trials in MCI and AD. These data were obtained from the Critical Path Institute's Critical Path for Alzheimer's Disease (CPAD) consortium, a public-private partnership funded in part by FDA, with aggregated data from MCI and AD clinical trials [3]. These studies were conducted between 1997 and 2015 and include 5526 control subjects. Due to the slowly evolving standard of care for MCI/AD, these historical controls provide a good source of data to predict the estimated outcome for the Renew NCP-5 study.

Table 1: Historical control subject dataset

Disease stage	# studies	# subjects	ADAS-Cog12 baseline statistics			
			min	Max	mean	std. dev.
mild/moderate AD	16	4897	4	75	31.1	10.0
MCI	2	629	2	57	17.1	8.2
total	18	5526	4	75	28.1	11.3

The CRBM longitudinally models a set of variables representing a subject's clinical state that includes cognitive measures (ADAS-Cog and MMSE), demographic and background information, and safety measures (laboratory tests and vital signs). Subject data are predicted in 3-month intervals, and because the CRBM is a probabilistic model, the set of digital twins for any single subject forms a distribution of predicted outcomes beyond baseline.



AD Digital Twin Example

Age (years): 69
Sex: Female
Region: Europe

ApoE e4 Count: 1
Taking donepezil: Yes
Height (cm): 160

	Time (months)	Baseline	3	6	9	12	15	18	21	24	27	30	33	36
ADAS	ADAS Commands	0	0	0	0	0	1	0	1	1	0	1	1	1
	ADAS Comprehension	0	1	0	0	0	0	0	0	0	1	0	0	0
	ADAS Construction	1	0	0	0	0	0	0	0	0	0	1	0	0
	ADAS Delayed Word Recall	9	6	10	9	8	10	10	10	10	10	10	10	10
	ADAS Ideational	2	1	0	0	0	0	0	0	0	2	1	1	0
	ADAS Naming	0	1	0	1	0	0	0	0	0	0	0	0	1
	ADAS Orientation	3	2	3	4	2	2	1	3	6	5	5	4	2
	ADAS Remember Instructions	0	0	0	1	0	0	0	0	0	0	0	1	1
	ADAS Spoken Language	0	0	0	0	0	0	0	0	0	0	0	0	0
	ADAS Word Finding	1	1	0	0	0	0	0	0	0	0	0	1	0
	ADAS Word Recall	5	2	5	5	5	5	6	5	9	6	6	6	6
	ADAS Word Recognition	0	5	4	6	7	7	10	9	12	7	9	11	10
	ADAS Total	21	19	22	26	22	25	27	28	38	31	33	35	31
MMSE	MMSE Attention Calculation	4	2	2	2	5	2	0	1	2	2	1	1	0
	MMSE Language	7	8	9	8	7	9	8	9	8	8	7	7	8
	MMSE Orientation	8	5	4	5	9	6	10	4	2	5	5	5	6
	MMSE Recall	2	0	1	0	1	2	1	1	0	0	0	0	0
	MMSE Registration	3	3	3	3	3	3	3	3	3	3	3	3	3
	MMSE Total	24	18	19	18	25	22	22	18	15	18	16	16	17
Clinical	Weight (kg)	47	46	49	47	41	43	44	49	52	50	46	42	46
	Systolic Blood Pressure (mmHg)	72	67	72	63	90	81	77	73	60	63	74	70	75
	Diastolic Blood Pressure (mmHg)	148	122	130	127	114	159	125	123	121	130	135	132	121
	Heart Rate (bpm)	71	65	68	60	76	71	66	68	60	60	67	58	63
Biomarkers	Alanine Aminotransferase (u/l)	15.8	10.5	9.8	17.4	30.2	13.3	14.0	13.4	13.7	14.5	13.6	22.0	19.0
	Alkaline Phosphatase (u/l)	56.3	63.5	55.8	70.5	75.0	62.2	78.4	73.2	68.4	85.4	79.7	83.6	90.9
	Aspartate Aminotransferase (u/l)	20.1	20.7	27.3	20.3	28.1	17.6	17.9	26.9	18.6	19.1	20.8	18.0	18.9
	Cholesterol (mmol/l)	6.5	6.7	6.2	4.2	4.6	5.0	5.6	5.1	4.9	4.7	5.4	5.0	4.5
	Creatine Kinase (u/l)	86.5	158.3	66.8	64.4	58.5	120.2	186.0	122.2	114.3	146.1	61.6	38.2	50.5
	Creatinine (mg/dl)	0.6	0.7	0.7	0.8	0.9	1.0	1.2	1.4	1.3	1.2	0.9	0.9	0.7
	Eosinophils (1e9/l)	0.1	0.0	0.1	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.2	0.0
	Gamma Glutamyl Transferase (u/l)	12.2	7.9	17.1	19.0	30.0	17.6	15.7	11.1	7.7	7.2	8.7	8.4	10.1
	Glucose (mmol/l)	6.6	3.4	4.5	4.4	5.2	4.2	3.9	3.0	4.4	3.3	4.4	5.4	3.9
	Hematocrit (%)	40.6	40.1	37.6	39.0	39.8	38.5	39.6	38.8	34.4	34.1	35.7	39.1	36.2
	Hemoglobin (g/dl)	12.9	12.8	12.6	13.0	13.2	12.2	12.1	12.0	11.6	10.4	11.0	11.8	11.6
	Hemoglobin A1C (%)	6.2	5.3	5.0	5.1	5.4	5.6	5.8	5.7	5.5	5.3	5.7	5.5	5.4
	Indirect Bilirubin (mg/dl)	0.4	0.3	0.5	0.6	0.6	0.6	0.6	0.9	1.0	0.6	0.7	0.5	0.5
	Lymphocytes (1e9/l)	1.3	1.0	1.3	1.3	1.1	1.2	1.2	0.9	1.1	1.3	1.3	1.1	1.1
	Monocytes (1e9/l)	0.3	0.4	0.2	0.2	0.3	0.2	0.4	0.4	0.4	0.6	0.3	0.2	0.4
	Platelet (1e9/cl)	2.2	2.1	2.2	2.7	4.1	2.9	2.7	2.5	3.0	2.6	2.4	3.0	3.4
	Potassium (meq/l)	4.3	5.1	4.8	4.5	4.4	4.8	4	4.3	4.5	3.9	4.2	4.2	4.6
	Sodium (meq/l)	144.4	143	146.1	142.2	139.5	145.9	146.3	137.4	139.4	136.9	138.7	143.3	145.8
	Triglycerides (g/l)	1.3	1.2	2.3	3.1	2	1.4	0.8	0.7	1	0.9	0.8	1.2	0.7

AD Digital Twin Example

Age (years): 69
Sex: Female
Region: Europe

ApoE e4 Count: 1
Taking donepezil: Yes
Height (cm): 160

	Time (months)	Baseline	3	6	9	12	15	18	21	24	27	30	33	36
ADAS	ADAS Commands	0	0	1	0	0	0	0	0	0	1	1	0	0
	ADAS Comprehension	0	2	0	0	0	0	0	0	0	0	1	0	0
	ADAS Construction	1	1	0	0	0	0	1	0	1	1	0	0	0
	ADAS Delayed Word Recall	9	9	8	10	10	10	8	10	10	9	10	5	10
	ADAS Ideational	2	0	2	0	0	0	0	0	0	0	1	2	0
	ADAS Naming	0	1	0	0	0	1	1	1	0	1	0	1	0
	ADAS Orientation	3	2	2	5	2	0	2	0	2	2	3	4	4
	ADAS Remember Instructions	0	0	0	1	0	0	0	0	1	0	0	1	0
	ADAS Spoken Language	0	0	0	0	0	0	0	0	0	0	1	0	0
	ADAS Word Finding	1	1	0	1	0	0	0	0	0	0	0	1	0
	ADAS Word Recall	5	5	6	6	5	5	5	5	5	5	5	6	5
	ADAS Word Recognition	0	6	8	12	12	12	8	3	6	7	9	10	5
	ADAS Total	21	27	27	35	29	28	25	19	25	26	32	30	24
MMSE	MMSE Attention Calculation	4	1	4	2	5	4	4	4	4	4	4	2	2
	MMSE Language	7	6	7	9	9	9	9	9	9	9	8	9	9
	MMSE Orientation	8	6	6	9	9	5	8	6	9	8	9	5	6
	MMSE Recall	2	0	0	0	1	1	0	1	2	0	1	0	1
	MMSE Registration	3	3	3	3	3	3	3	3	3	3	3	3	3
	MMSE Total	24	16	20	23	27	22	24	23	27	24	25	19	21
Clinical	Weight (kg)	47	47	45	49	48	44	45	46	48	53	51	52	55
	Systolic Blood Pressure (mmHg)	72	75	82	74	65	66	70	74	85	92	69	69	82
	Diastolic Blood Pressure (mmHg)	148	168	139	139	126	125	106	140	143	117	114	142	158
	Heart Rate (bpm)	71	64	65	73	78	79	60	61	57	63	54	63	67
Biomarkers	Alanine Aminotransferase (u/l)	15.8	20.2	17.2	14.9	20.4	20.1	10.8	10.0	11.0	11.9	14.5	16.9	16.7
	Alkaline Phosphatase (u/l)	56.3	63.7	48.0	48.1	61.2	52.6	37.2	45.4	50.0	47.1	61.9	69.5	61.3
	Aspartate Aminotransferase (u/l)	20.1	26.6	19.1	16.5	24.7	24.6	17.3	17.5	17.8	17.6	19.7	22.9	26.6
	Cholesterol (mmol/l)	6.5	5.5	5.9	5.2	6.4	5.5	7.3	7.0	6.5	6.0	6.4	6.6	7.2
	Creatine Kinase (u/l)	86.5	92.9	101.6	92.0	72.6	40.5	60.7	86.8	129.1	111.3	77.4	88.1	65.4
	Creatinine (mg/dl)	0.6	0.6	0.5	0.7	0.8	0.8	0.8	0.9	1.1	1.1	1.0	1.0	1.0
	Eosinophils (1e9/l)	0.1	0.2	0.1	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.2	0.3	0.2
	Gamma Glutamyl Transferase (u/l)	12.2	13.9	14.0	9.3	12.8	10.5	13.4	19.4	12.2	10.8	11.1	15.8	11.5
	Glucose (mmol/l)	6.6	5.8	5.5	5.9	5.3	5.0	4.3	4.1	4.1	4.3	5.4	7.4	6.2
	Hematocrit (%)	40.6	40.6	39.3	37.8	40.0	37.9	37.3	35.1	35.0	31.1	37.5	39.9	36.1
	Hemoglobin (g/dl)	12.9	13.4	13.1	12.9	13.4	12.6	12.4	11.3	11.2	10.6	11.8	12.7	12.5
	Hemoglobin A1C (%)	6.2	6.3	5.8	5.5	5.7	6.0	6.0	5.9	5.7	5.3	5.7	6.4	6.4
	Indirect Bilirubin (mg/dl)	0.4	0.5	0.7	0.6	0.8	0.6	0.6	0.5	0.6	0.7	1.0	1.0	0.8
	Lymphocytes (1e9/l)	1.3	1.1	1.1	1.6	1.3	1.1	1.3	1.1	1.4	1.7	2.2	1.8	2.2
	Monocytes (1e9/l)	0.3	0.1	0.3	0.5	0.4	0.5	0.3	0.3	0.4	0.3	0.3	0.4	0.7
	Platelet (1e9/cl)	2.2	2.4	2.2	2.4	3.0	2.9	2.4	2.3	3.0	2.5	2.9	3.1	3.1
	Potassium (meq/l)	4.3	4.4	4.8	4.2	4.3	4.9	4.6	5.2	4.7	4.8	4.9	5.2	5.1
	Sodium (meq/l)	144.4	142.9	147.4	142.1	141.6	141	142.9	142.6	140	144.5	142	142	138.8
	Triglycerides (g/l)	1.3	2	0.7	0.7	1.3	2.2	1.2	1	1	1.1	1	1.4	0.9

Figure 1. A pair of example digital twins. The two subjects have the same baseline data, but different follow-up data beyond baseline that are sampled from the probabilistic distribution modeled by the CRBM.

The CRBM was trained on 3868 subjects from the CPAD dataset, with the remaining 1658 subjects making up a test dataset used for evaluating the ML model's performance. The methods used to train the ML model follow the same methods discussed in recent publications [1,2].

For each actual subject in the test dataset, a digital twin with matched baseline characteristics was generated, and their trajectories were simulated for 18 months. A variety of metrics were used (in italics below) to assess if the values determined from the model are consistent with those observed in the test dataset (this test dataset was not used for CRBM training).

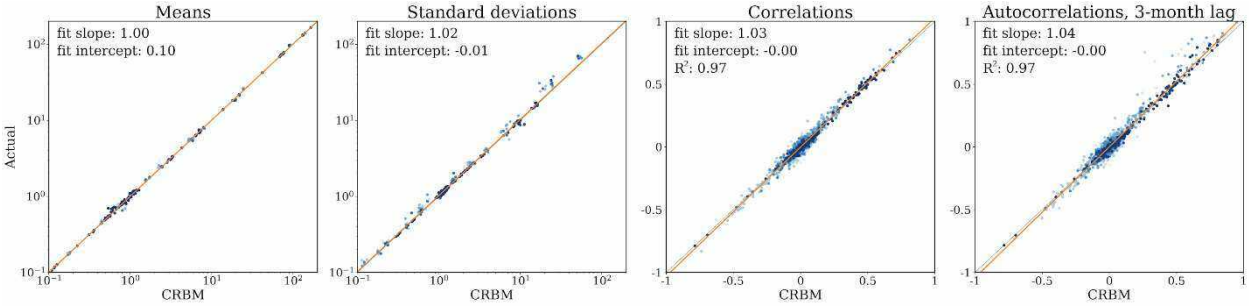


Figure 2. Comparison of statistics from actual data and digital twins at each follow-up visit over 18 months.

The digital twin trajectories correlated well with actual data. The *means, standard deviations, correlations, and autocorrelations* computed from the digital twins agreed with those from the actual subjects (Fig. 2). There were strong and similar equal-time correlations and lagged autocorrelations (3 and 6 months, the latter not shown) among variables, with R^2 of 0.97, 0.97 and 0.96, respectively, for model predictions versus actual data.

Because the CRBM model is trained on values of individual components of the cognitive test ADAS-Cog, it can simulate the evolution of any combination of these variables, including the 12-item ADAS-Cog score, commonly used as a measure of overall disease progression. Fig. 3 shows the distribution of ADAS-Cog 12 scores from actual data and digital twins over 18 months: both exhibit an almost identical gradual increase in the mean ADAS-Cog12 score with time, with a widening of the distribution over time.

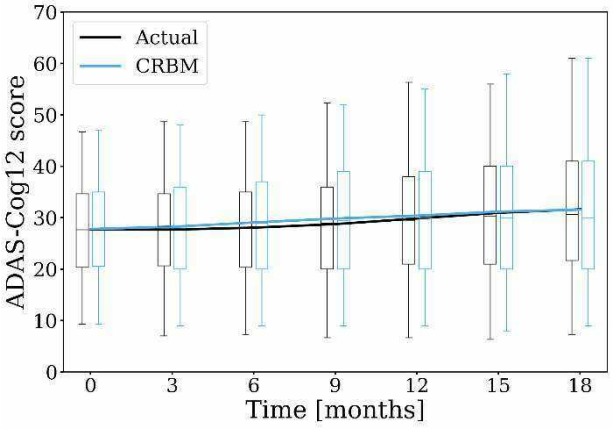


Figure 3. Comparison of actual and CRBM-derived ADAS-Cog12 score progression over 18 months. The box plot shows the mean score (the lines) and the 5th and 95th percentiles at each visit.

These results, and previous publications, indicate that the CRBM accurately models the historical controls in the test dataset and is capable of generating digital twins that are statistically indistinguishable from actual subjects. This gives confidence that the CRBM may be used to generate digital twins for similar subjects. In the case of the Renew NCP-5 study, the digital twins allow for analyses that measure the treatment effect relative to control subjects rather than an active sham arm.

Unlearn's digital twins derived from ML analyses of control arm subjects in historical clinical trial data have potential utility in overcoming some limitations of active sham arms in studies such as the Renew NCP-5 study. In some cases, it may be difficult to create an active sham that acts as a dummy treatment analogous with a placebo while maintaining blinding. This leaves open the possibility that an active sham, such as a device on a low setting, may have a treatment effect relative to standard-of-care. However, a two-arm study design does not enable one to answer, 1) whether the active sham device has an effect relative to standard-of-care, or 2) whether the treatment has an effect relative to standard-of-care. Instead, a two-arm study only addresses whether the treatment has an effect relative to the active sham.

In many cases, the historical record from drug trials provides rich data on control subjects with similar characteristics to the makeup of subjects enrolled in a study. Unlearn's digital twins, derived from historical studies, provide predictions for a control population that is exactly matched to the study population. These digital twins may be used to answer the above questions and provide a more complete picture of the treatment efficacy.

For each actual subject in the study, ten digital twins will be generated to form an external control group, with data predicted for the 12-week, 24-week, 9-month, and 12-month assessments. The exploratory analysis will compare, for each study arm, the digital twins in the external control arm to the treated subjects and estimate the effect on the ADAS-Cog12 progression from baseline.

The analysis of treatment effects with digital twins centers on paired difference estimates of the treatment effect for each subject:

$$\tau_i = y_i - E(y_i')$$

where τ_i is the paired difference estimate, y_i is the outcome for subject *i*, the change in ADAS-Cog12 score from baseline, and $E(y_i')$ is the average outcome over the set of ten digital twins for subject *i*. We regress the paired difference estimates for subjects in the treatment arm on two binary covariates: CVR risk score (low / medium vs high / very high) and disease stage (MCI vs AD). These covariates are centered, so that the intercept in this regression may be interpreted as the average effect of the treatment, compared with subjects who do not receive any therapy from the device studied.

Formally, for each subject i in the treatment group, we fit the following linear model:

$$\tau_i = \tau_{treatment} + \beta_{treatment,CVR}(u_i - \bar{u}_{treatment}) + \beta_{treatment,AD}(v_i - \bar{v}_{treatment}) + N(0, \sigma^2_{treatment})$$

Where $\tau_{treatment}$ is the average treatment effect, u_i is a binary variable equal to 0 if subject i has low / medium CVR and equal to 1 if subject i has high / very high CVR, $\bar{u}_{treatment}$ is the proportion of subjects in the treatment group who have high / very high CVR, v_i is a binary variable equal to 0 if subject i has MCI and equal to 1 if subject i has AD, and $\bar{v}_{treatment}$ is the proportion of subjects in the treatment group who have AD. The regression coefficients capture any heterogeneity in the treatment effect: $\beta_{treatment,CVR}$ represents the average treatment effect for patients with high / very high CVR minus the average treatment effect for patients with low / medium CVR, while $\beta_{treatment,AD}$ represents the average treatment effect for patients with AD minus the average treatment effect for patients with MCI. $\sigma^2_{treatment}$ is a nuisance parameter which captures the variance in the paired difference estimates. Using t-tests, we will compute p-values for testing whether each of $\tau_{treatment}$, $\beta_{treatment,CVR}$ and $\beta_{treatment,AD}$ are equal to zero, as well as a 95% confidence interval for $\tau_{treatment}$.

We fit the same regression on the active sham arm. For each subject j who receives the active sham treatment, we assume the linear model:

$$\tau_j = \tau_{sham} + \beta_{sham,CVR}(u_j - \bar{u}_{sham}) + \beta_{sham,AD}(v_j - \bar{v}_{sham}) + N(0, \sigma^2_{sham})$$

In this case, τ_{sham} represents the average effect of the active sham treatment, $\beta_{sham,CVR}$ represents the difference in the average effect of the active sham treatment between patients with high / very high vs low / medium CVR, and $\beta_{sham,AD}$ represents the difference in the average effect of the active sham treatment between patients with AD vs MCI. Again we compute p-values for testing whether each of τ_{sham}, $\beta_{sham,CVR}$ and $\beta_{sham,AD}$ are equal to zero, and a 95% confidence interval for τ_{sham}.

The primary and secondary endpoints of the Renew NCP-5 study allow for testing the hypothesis that the treatment provides a benefit over active sham. However, if the active sham therapy itself provides a beneficial effect relative to standard-of-care, then the statistical significance of the treatment may be reduced. This exploratory analysis allows for an evaluation of two additional hypotheses: 1) that the treatment has a benefit over subjects not receiving any therapy from the device studied, and 2) that the active sham treatment provides no benefit over subjects not receiving any therapy from the device studied. Further, we investigate whether each of these benefits (if they exist) varies according to patients' CVR scores or between sufferers of MCI vs AD.

These hypotheses are evaluated using digital twins created from a statistical model trained on historical control arm data from control groups of previously completed MCI and AD drug trials. The analysis has limitations if the subjects in the Renew NCP-5 study are fundamentally different from the subjects in the historical control dataset, for example if unobserved confounders exist affecting disease progression differently between the two groups.

13.16 Proportion of Patients with vADAS Responder at Post-Treatment Visits at 6, 12, 18, 24 Weeks, as well as 9 and 12 Months.

The responder is defined as the vADAS change from baseline score (timepoint – baseline) <= -2 and below at each post-baseline visit.

For subjects not impacted by COVID-19, there will be no imputation for the missing data, and subjects with missing data will have the status of non-responder. For subjects who have been impacted by COVID-19, the following methods will be used:

- Not COVID-19 related, site closure: the subject will be included in the analysis with multiple imputation used to account for missing response.
- COVID-19 infection: the subject will be considered a non-responder from the timepoint of COVID-19 infection.

- COVID-19 related, missing: the subject will be included in the analysis with multiple imputation used to account for missing response status.
- COVID19- related, non-missing: the vADAS scores after the COVID-19 disruption will be used.

The number and proportion of responders will be summarized along with a 95% exact (Clopper-Pearson) confidence interval for the proportion. The analysis of proportion of the responders at each post-baseline visit will use CMH weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference. Stratification for the analysis will use the actual stratification factor value if the subject is misclassified during the randomization. The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19. The subgroup analyses will be performed using an unstratified chi-square test with ITT population within each subgroup factor described in section 4.

13.17 The Average of the Change from Baseline in vADAS-Cog Score at 12, 18 and 24 weeks after Initiation of Treatment

This is the same as the primary endpoint. It will be analyzed using the method 2) described in section 13 and the missing data will be handled using the method described in section 11.2. The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19. The subgroup analyses will be performed using the same method with ITT population within each subgroup factor described in section 4. In addition, sub-group analysis will be performed for significant co-morbidities (diabetes, sleep disorders, mental health disorders, and thyroid disorders) and significant concurrent medications (thyroid, sedation, cognition/memory, and antidepressants/anti-anxiety medications).

13.18 ADCS-CGIC Follow-up

The descriptive summary of frequency count and percentage in ADCS-CGIC results (Marked Improvement, Moderate Improvement, Minimal Improvement, No Change, Minimal Worsening, Moderate Worsening, and Marked Worsening) at 24 weeks, 9 months and 12 months will be provided by treatment group.

See Section 11.1 for details regarding the handling of missing data and COVID-19 impact.

For the inferential statistical analyses of the response at each visit, see Section 11.1.

The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19 (i.e. will not contribute to the numerator or denominator). The subgroup analyses will be

performed using the same method with ITT population within each subgroup factor described in section 4.

13.19 Executive Function Assessed by Trail Making Test B Follow-up

The observed score at each scheduled time point, change from baseline in executive function at 24 weeks, 9 months and 12 months will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

The change from baseline will be analyzed using the method 1) described in section 13. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19. The subgroup analyses will be performed using the same method with ITT population within each subgroup factor described in section 4.

13.20 ADAS-Cog14 Follow-up

The observed and change from baseline in vADAS Cog scores at 24 weeks, 9 months, and 12 months will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The change from baseline will be analyzed using the method 1) described in section 13. The missing data will be handled by MMRM ANCOVA model and there is no imputation for missing data implemented.

13.21 The Average of the Change from Baseline in ADCS-ADL at 12, 18 and 24 weeks after Initiation of Treatment

This is the same as the secondary endpoint for ADCS-ADL. It will be analyzed using the method 2) described in section 13 and the missing data will be handled using the method described in section 11.2. The same analysis will be repeated using PP population as sensitivity analysis. In addition, the same analysis will be performed using ITT population with excluding the data from the subjects impacted by COVID-19. The subgroup analyses will be performed using the same method with ITT population within each subgroup factor described in section 4.

14. Tables, Listings and Figures

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15. Changes in Stastical Analysis Plan from the Protocol

1. The exploratory endpoint, endothelial function via flow-mediated dilation (FMD), is not included in the SAP because the endpoint was not collected at any site.
2. The exploratory endpoint, arterial stiffness via pulse wave velocity (PWV), is not included in the SAP because the endpoint was not collected at any site.
3. The payor based endpoint, change in ability to drive, is not included in the SAP because the endpoint was not collected at any site.

16. References

1. Machine learning for comprehensive forecasting of Alzheimer's Disease progression, CK Fisher et al, Scientific Reports 9:13622 (2019).

2. Generating Digital Twins with Multiple Sclerosis Using Probabilistic Neural Networks, JR Walsh et al, bioRxiv:934679, https://doi.org/10.1101/2020.02.04.934679.
3. Neville, J. et al. Development of a unified clinical trial database for Alzheimer's disease. Alzheimer's & Dementia: journal Alzheimer's Assoc. 11, 1212–1221 (2015).

APPENDIX B2: Table Shells

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17. Table Shells

General Table Programming Notes:

- Display visits that appear per schedule in the protocol.
- Abbreviations used in a table should be displayed in alphabetical order in the first line after the footer line.

Table 14.1.1
Subject Disposition
(All Subjects)

Number of Subjects	Renew NCP-5 N=XX n (%)	Active sham N=XX n (%)	Overall N=XX n (%)
Screened			xx
Screen Failure			xx
ITT Population	wx	xx	xx
PP Population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Study	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from Study	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Discontinued from Study			
Reason #1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason #2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason #3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason #4	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason #5	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.			

Note: Percentages are based on the number of subjects in the treatment group or overall of ITT population.

Cross References: Listings 16.2.1.1, 16.2.1.2

Table 14.1.2
Demographics and Baseline Characteristics
(Intent-to-Treat)

	Renew NCP-5 N=xx	Active sham N=xx	Overall N=xx
Age (years)			
n	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Height (cm)			
n	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Weight (kg)			
n	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Body Mass Index (kg/m^2)			
n	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Sex, n (%)			
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race, n (%)			
American Indian or Alaska Native	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity, n (%)			
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)

Educational Level, n (%)			
9th - 12th grade, No diploma	xx (xx.x)	xx (xx.x)	xx (xx.x)
High School Diploma or Equivalent	xx (xx.x)	xx (xx.x)	xx (xx.x)
Some College, No Degree	xx (xx.x)	xx (xx.x)	xx (xx.x)
College Degree	xx (xx.x)	xx (xx.x)	xx (xx.x)
Graduate or Professional Degree	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cognitive decline, n (%)			
Mild Cognitive Impairment due to Alzheimer's Disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild Dementia of the Alzheimer's Type	xx (xx.x)	xx (xx.x)	xx (xx.x)
CVR Score, n (%)			
High/Very High Risk	xx (xx.x)	xx (xx.x)	xx (xx.x)
Low/Medium Risk	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: Max = Maximum, Min = Minimum, cm = centimeters, kg = kilograms, m = meters,SD = Standard Deviation.
Note: Percentages are based on the number of subjects in the treatment group or overall in safety population.

Cross References: Listing 16.2.4.2, 16.2.4.3, 16.2.4.5

Table 14.1.3
Prior and Concomitant Medications
(Intent-to-Treat)

Preferred Term (WHOATC Text)	Renew NCP-5 (N=XX) n (%)	Active sham(N=XX) n (%)	Overall(N=XX) n (%)
Subjects with Any Medications	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.			

Note: Percentages are based on the number of subjects in the treatment group.
Medications are coded using the WHO Drug Dictionary (WHODRUG, version WHO-DD B3/C3).
Any medication that has a start date, stop date on or after the first treatment is considered a concomitant medication.
Cross References: Listing 16.2.4.6

Table 14.2.1
Integrated Change From Baseline on vADAScog
(Intent-to-Treat)

This analysis is described in Appendix A1 and will be a Bayesian analysis.

Integrated Change From Baseline on vADAScog	Posterior Mean	Posterior Median	Posterior Standard Deviation	Posterior 95% Credible Interval
Renew NCP-5 Arm				
Active sham Arm				
Difference Renew NCP-5 minus Active sham				
Posterior Probability Superiority of Renew NCP-5 over Active sham				

Table 14.2.2.1.1
Analysis of ADCS-CGIC: ITT
(Intent-to-Treat)

Time Point ADCS-CGIC Rating	Renew NCP-5 (N=xx) n (%)	Active sham (N=xx) n (%)
Week 12		
Marked improvement	xx (xx.x)	xx (xx.x)
Moderate improvement	xx (xx.x)	xx (xx.x)
Minimal improvement	xx (xx.x)	xx (xx.x)
No change	xx (xx.x)	xx (xx.x)
Minimal worsening	xx (xx.x)	xx (xx.x)
Moderate worsening	xx (xx.x)	xx (xx.x)
Marked worsening	xx (xx.x)	xx (xx.x)
Common Odd Ratio	xx.x	
95% Confidence Interval of Odds Ratio	xx.x, xx.x	
p-value	0.xxx	
Repeat for Week 18. Week 24, etc.		

Cross References: Listing 16.2.6.2.2

Table 14.2.2.1.2
Analysis of ADCS-CGIC: Per Protocol
(Per-Protocol)

Table 14.2.2.1.3
Analysis of ADCS-CGIC Excluding the Data from Subjects Impacted by COVID-19
(Intent-to-Treat)

Table 14.2.2.1.4
Analysis of ADCS-CGIC Subgroup by Cognitive Decline
(Intent-to-Treat)

Table 14.2.2.1.5
Analysis of ADCS-CGIC Subgroup by CVR Score
(Intent-to-Treat)

Table 14.2.2.2.1
Analysis of Executive Function Assessed by Trail Making Test B
(Intent-to-Treat)

Time Point	Renew NCP-5 (N=xx)		Active sham (N=xx)	
Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline				
n	xx		xx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx, xx		xx, xx	
Week 12				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Repeat for weeks 18 and 24				
Average of Change from baseline				
n		xx		xx
Mean (SD)		xx.x (xx.xx)		xx.x (xx.xx)
Median		xx.x		xx.x
Min, Max		xx, xx		xx, xx
Overall Comparison of Average of Change from Baseline (Renew NCP-5 vs. Active sham)				
LS Mean (SE)		xx.xx (x.xxx)		
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Overall p-values for Other Terms				
Baseline Value		0.xxx		
Treatment quality		0.xxx		
Cognitive decline		0.xxx		
CVR score		0.xxx		
ApoE		0.xxx		

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.

Note: Average of change from baseline in Executive Function score as a continuous variable is based on analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), ApoE (positive vs. negative), treatment group.

Cross References: Listing 16.2.6.1.1

Table 14.2.2.2.2
Analysis of Executive Function Assessed by Trail Making Test B
(Per-Protocol)

Table 14.2.2.2.3
Analysis of Executive Function Assessed by Trail Making Test B Excluding the Data from Subjects Impacted by COVID-19
(Intent-to-Treat)

Table 14.2.2.2.4
Analysis of Executive Function Assessed by Trail Making Test B Subgroup by Cognitive Decline
(Intent-to-Treat)

Table 14.2.2.2.5
Analysis of Executive Function Assessed by Trail Making Test B Subgroup by CVR Score
(Intent-to-Treat)

Table 14.2.2.3
Integrated Change From Baseline on ADCS-ADL
(Intent-to-Treat)

Integrated Change From Baseline on ADCS-ADL	Posterior Mean	Posterior Median	Posterior Standard Deviation	Posterior 95% Credible Interval
Renew NCP-5 Arm				
Active sham Arm				
Difference Renew NCP-5 minus Active sham				
Posterior Probability Superiority of Renew NCP-5 over Active sham				

Table 14.2.2.4
Integrated Change From Baseline on ADAScog-14
(Intent-to-Treat)

Integrated Change From Baseline on ADAScog-14	Posterior Mean	Posterior Median	Posterior Standard Deviation	Posterior 95% Credible Interval
Renew NCP-5 Arm				
Active sham Arm				
Difference Device minus Active sham				
Posterior Probability Superiority of Device over Active sham				

Table 14.2.3.1.1 Analysis of vADAS Cog Follow-up Score (ITT Population)

Time Point	Renew NCP-5 (N=xx)		Active sham (N=xx)	
Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline				
n	xx		xx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx, xx		xx, xx	
Week 24				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
By visit analysis [1]				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Month 9				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
By visit analysis [1]				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Month 12				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
By visit analysis [1]				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)

Difference in LS Mean (SE)	xx.xx (x.xxx)	
95% Confidence Interval for Difference	(xx.xx, xx.xx)	
p-value	0.xxx	
Overall Comparison of Change from Baseline (Renew NCP-5 vs. Active sham) [1]		
LS Mean (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
Difference in LS Mean (SE)	xx.xx (x.xxx)	
95% Confidence Interval for Difference	(xx.xx, xx.xx)	
p-value	0.xxx	
Overall p-values for Other Terms [1]		
Baseline Value	0.xxx	
Treatment quality	0.xxx	
Cognitive decline	0.xxx	
CVR score	0.xxx	
ApoE	0.xxx	
Time point	0.xxx	
Time point*Treatment	0.xxx	

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
[1] Change from baseline in vADAS Cog Scores as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), ApoE (positive vs. negative), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.3.1.2 Analysis of vADAS Cog Follow-up Scores (Per-Protocol Population)

Use layout of 14.2.3.1

Table 14.2.3.1.3 Analysis of vADAS Cog Follow-up Scores: Excluding the Data from Subjects Impacted by COVID-19 (ITT Population)

Use layout of 14.2.3.1

Table 14.2.3.1.4 Analysis of vADAS Cog Follow-up Scores: Subgroup by Cognitive Decline (ITT Population)

Table 14.2.3.1.5 Analysis of vADAS Cog Follow-up Scores: Subgroup by CVR Score (ITT Population)

Use layout of 14.2.3.1

Table 14.2.3.2.1
Analysis of ADCS-ADL Follow-up Scores
(ITT Population)

Use layout of 14.2.3.1

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
[1] Change from baseline in ADCS-ADL Scores as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.3.2.2
Analysis of ADCS-ADL Follow-up Scores
(Per Protocol Population)

Use layout of 14.2.3.1

Table 14.2.3.2.3
Analysis of ADCS-ADL Follow-up Scores: Excluding the Data from Subjects Impacted by COVID-19
(ITT Population)

Use layout of 14.2.3.1

Table 14.2.3.2.4
Analysis of ADCS-ADL Follow-up Scores: Subgroup by Cognitive Decline
(ITT Population)

Use layout of 14.2.3.1

Table 14.2.3.2.5
Analysis of ADCS-ADL Follow-up Scores: Subgroup by CVR Score
(ITT Population)

Use layout of 14.2.3.1

Table 14.2.3.3
Analysis of Fall Risk Assessment/Functional Reach Test/TUG Test Scores
(ITT Population)

Use layout of 14.2.3.1

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
[1] Change from baseline in Fall Risk Assessment/Functional Reach Test/TUG Test Scores as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value,treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.
[2] Average of change from baseline in Fall Risk Assessment/Functional Reach Test/TUG Test Scores as a continuous variable is based on analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group.

Cross References: Listing 16.2.6.1.1

Table 14.2.3.4
Analysis of NPI Aggression Index Scores
(ITT)

Use layout of 14.2.3.1

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.

Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
[1] Change from baseline in NPI Aggression Index Scores as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.
[2] Average of change from baseline in NPI Aggression Index Scores as a continuous variable is based on analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group.

Cross References: Listing 16.2.6.1.1

Table 14.2.3.5
Analysis of QOL/Patient Survey Scores
(ITT)

Time Point Survey Question	Renew NCP-5 (N=XX) n (%)	Active sham (N=XX) n (%)
Month 12		
How well would you rate your sleep?		
Answer #1	xx (xx.x)	xx (xx.x)
Answer #2	xx (xx.x)	xx (xx.x)
Answer #3	xx (xx.x)	xx (xx.x)
Answer #4	xx (xx.x)	xx (xx.x)
Etc.		
How much anxiety do you have?		
Answer #1	xx (xx.x)	xx (xx.x)
Answer #2	xx (xx.x)	xx (xx.x)
Answer #3	xx (xx.x)	xx (xx.x)
Etc.		

Abbreviations: QOL = Quality of Life.
Note: Percentages are based on the number of safety population in the treatment group.

Cross References: Listing 16.2.6.1.1

Table 14.2.3.6.1
Payor-Based Summary of Resource Use Inventory Completion
(Intent-to-Treat)

Time Point	Renew NCP-5 (N=XXX)	Active sham (N=XXX)
Baseline		
Requested, n (%)	xx (x.x)	xx (x.x)
Responded[b,c], n (%)	xx (x.x)	xx (x.x)
Completed[c], n (%)	xx (x.x)	xx (x.x)
Repeat "Baseline" statistics for the following visits		
Month 3		
Month 6		
Month 9		
Month 12		
Total RUI follow-up time, post baseline		
Mean (SD)	x.x (x.xx)	x.x (x.xx)
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)
Range	xx - xx	xx - xx

IQR, interquartile range; n, number of subjects who had at least one visit; RUI, resource use inventory.
a Percentages are based on N, the number of subjects overall or within the treatment group.
b Subjects who provided at least one response to the RUI at the visit are included herein.
c Percentages are based on the number of subjects for whom the RUI was provided, "Requested", at that visit.

Table 14.2.3.6.2.1
Payor-Based Summary of Inpatient Stays
(Intent-to-Treat)

Estimate	Renew NCP-5 (N=XXX)	Active sham (N=XXX)	p-value
Inpatient Stays			
Total, post baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Annual Rate (95% CI)[a]	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
IRR (95% CI) Renew vs. Active sham	x.xx (x.xx, x.xx)		0.xxx
3 months prior to baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Repeat "3 months prior to baseline" statistics for the following periods			
Baseline to 3 months			
Month 3 to 6			
Month 6 to 9			
Month 9 to 12			
Length of Inpatient Stays (nights)			
Total, post baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Annual Rate (95% CI)[a]	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
3 months prior to baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	

Estimate	Renew NCP-5 (N=XXX)	Active sham (N=XXX)	p-value
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Repeat "3 months prior to baseline" statistics for the following periods			
Baseline to 3 months			
Month 3 to 6			
Month 6 to 9			
Month 9 to 12			
Reason for admission			
Reason #1, n (%)			
Reason #2, n (%)			
Reason #3, n (%)			
….			
Reason #n, n (%)			

CI, Confidence Interval; IQR, interquartile range; IRR, Incidence Rate Ratio; n, number of subjects who had at least one visit.
a Available data extrapolated to 12 months.
b Based on number of inpatient stays.
c Percentages are based on the number of subjects overall or within the treatment group.

Table 14.2.3.6.2.2
Payor-Based Summary of Inpatient Stays by Cognitive Decline

(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.2.1 for Cognitive decline (MCI due to AD vs. mild AD).

Table 14.2.3.6.2.3
Payor-Based Summary of Inpatient Stays by CVR Score

(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.2.1 for CVR score (low/medium vs. high/very high).

Table 14.2.3.6.3.1
Payor-Based Summary of Outpatient Clinician Visits
(Intent-to-Treat)

Estimate	Renew™ NCP-5 (N=XXX)	Active sham (N=XXX)	p-value
Doctor Visits			
Total, post baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Annual Rate (95% CI)[a]	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
IRR (95% CI) Renew vs. Active sham	x.xx (x.xx, x.xx)		0.xxx
3 months prior to baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Repeat "3 months prior to baseline" statistics for the following periods			
Baseline to 3 months			
Month 3 to 6			
Month 6 to 9			
Month 9 to 12			
Repeat "Doctor Visits" statistics for each outpatient clinician visit type and across all clinician types (Total)			
Nurse Visits			
<Other>			
Total			

CI, Confidence Interval; IQR, interquartile range; IRR, Incidence Rate Ratio; n, number of subjects who had at least one visit.
a Available data extrapolated to 12 months.

Table 14.2.3.6.3.2
Payor-Based Summary of Outpatient Clinician Visits by Cognitive Decline
(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.3.1 for Cognitive decline (MCI due to AD vs. mild AD).

Table 14.2.3.6.3.3
Payor-Based Summary of Outpatient Clinician Visits by CVR Score
(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.3.1 for CVR score (low/medium vs. high/very high).

Table 14.2.3.6.4.1
Payor-Based Summary of Durable Medical Equipment
(Intent-to-Treat)

Estimate	Renew™ NCP-5 (N=XXX)	Active sham (N=XXX)	p-value
Eye Glasses			
Annualized[a]			
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Repeat "Eye Glasses" statistics for the following items			
Contact Lenses			
…			
<Other>			

CI, Confidence Interval; IQR, interquartile range; IRR, Incidence Rate Ratio; n, number of subjects who had at least one visit; N, total post baseline.
a Available data extrapolated to 12 months.

Programming Note: All medical equipment items captured in question 3 of the RUI should be included herein. If the equipment was not utilized then the continuous summary statistics do not need to be displayed.

Table 14.2.3.6.4.2
Payor-Based Summary of Durable Medical Equipment by Cognitive Decline
(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.4.1 for Cognitive decline (MCI due to AD vs. mild AD).

Table 14.2.3.6.4.3
Payor-Based Summary of Durable Medical Equipment by CVR Score
(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.4.1 for CVR score (low/medium vs. high/very high.

Table 14.2.3.6.5.1
Payor-Based Summary of Overnight Care
(Intent-to-Treat)

Estimate	Renew™ NCP-5 (N=XXX)	Active sham (N=XXX)	p-value
Overnight Care (nights)			
Total, post baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Annual Rate (95% CI)[a]	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
IRR (95% CI) Renew vs. Active sham	x.xx (x.xx, x.xx)		0.xxx
3 months prior to baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Repeat "3 months prior to baseline" statistics for the following periods			
Baseline to 3 months			
Month 3 to 6			
Month 6 to 9			
Month 9 to 12			

CI, Confidence Interval; IQR, interquartile range; IRR, Incidence Rate Ratio; n, number of subjects who had at least one visit.
a Available data extrapolated to 12 months.

Table 14.2.3.6.5.2
Payor-Based Summary of Overnight Care by Cognitive Decline
(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.5.1 for Cognitive decline (MCI due to AD vs. mild AD).

Table 14.2.3.6.5.3
Payor-Based Summary of Overnight Care by CVR Score

(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.5.1 for CVR score (low/medium vs. high/very high).

Table 14.2.3.6.6.1
Payor-Based Summary of Paid Individual Care (hours)

(Intent-to-Treat)

Estimate	Renew™ NCP-5 (N=XXX)	Active sham (N=XXX)	p-value
Paid Individual Care			
Total, post baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Annual Rate (95% CI)[a]	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
IRR (95% CI) Renew vs. Active sham	x.xx (x.xx, x.xx)		0.xxx
3 months prior to baseline			
N	(N=XXX)	(N=XXX)	
n (%)	xx (x.x)	xx (x.x)	
Mean (SD)	x.x (x.xx)	x.x (x.xx)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)	
Range	xx - xx	xx - xx	
Repeat "3 months prior to baseline" statistics for the following periods			
Baseline to 3 months			
Month 3 to 6			
Month 6 to 9			
Month 9 to 12			

CI, Confidence Interval; IQR, interquartile range; IRR, Incidence Rate Ratio; n, number of subjects who had at least one visit.
a Available data extrapolated to 12 months.

Table 14.2.3.6.6.2
Payor-Based Summary of Paid Individual Care (hours) by Cognitive Decline

(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.6.1 for Cognitive decline (MCI due to AD vs. mild AD).

Table 14.2.3.6.6.3
Payor-Based Summary of Paid Individual Care (hours) by CVR Score

(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.6.1 for CVR score (low/medium vs. high/very high).

Table 14.2.3.6.7
Payor-Based Unit Costs for Healthcare Resource Use

Medical Resource	2020 US $	Source
DIRECT MEDICAL COSTS		
Prescription Medication (cost per diem dosage)		Average Sale Price (ASP; 20XX) *Medicare's average sales price rates from the most recent quarterly data available*
Medication 1		
Medication 2 …		
Medication X		
Inpatient Stay (cost per night)		5% SAF Inpatient FY 2019
Hospitalization 1		
Hospitalization 2 …		
Hospitalization X		
Outpatient Clinician Visit (cost per visit)		MPFS FY 2019
General practitioner		
Geriatrician		
Neurologist		
Nurse practitioner or physician assistant		
Occupational therapist		
Physical therapist		
Psychologist		
Social worker		
<Other provider>		
Emergency Room Visit (cost per visit)		HOPPS FY 2019
Durable Medical Equipment (cost per item)		DMEPOS FY 2019
Eye Glasses		
Contact Lenses		
Hearing Aids		
Dentures		
Joint Brace		
Elastic Stockings		

Medical Resource	2020 US $	Source
Cane/Walking Stick		
Crutches		
Walker		
Restraints		
Wheel Chair		
Lift Chair (electric)		
Safety Bars		
Toilet Bars		
Toilet Seat/Chair		
Tub Transfer Bench		
Shower Bench		
Handrails for Shower		
Hospital Bed		
Bed Pads		
Bed Alarm		
Urinary Catheter		
Door Alarms		
Diapers/Pads/Briefs		
<Other>		
DIRECT NON-MEDICAL COSTS		
Overnight Care		
Home health aide/attendant/companion/other paid individual (cost per day)		Genworth
Home health aide/attendant/companion/other paid individual (cost per hour)		

Programming Note: Only costs for medical equipment and physician office visits used by at least one subject in the study should be included on the table.

Table 14.2.3.6.8.1.
Payor-Based Average Annualized Cost per Subject
(Intent-to-Treat)

Estimate	Renew NCP-5 (N=XXX)	Active sham (N=XXX)	LSM Difference (Renew-Active sham) (95% CI)	p-value
Prescription Medications				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Inpatient Stays				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Outpatient Clinician Visits				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Emergency Room Visits				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Durable Medical Equipment				

Estimate	**Renew NCP-5 (N=XXX)**	**Active sham (N=XXX)**	**LSM Difference (Renew-Active sham) (95% CI)**	**p-value**
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Total Direct Medical Costs				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Overnight Care				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Paid Individual Care				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Total Direct Non-medical Costs				
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		
Total Direct Costs				

Estimate	Renew NCP-5 (N=XXX)	Active sham (N=XXX)	LSM Difference (Renew-Active sham) (95% CI)	p-value
n	xx	xx		
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.x – x.x)	0.xxx
Median (IQR)	x.x (x.x – x.x)	x.x (x.x – x.x)		
Range	xx - xx	xx - xx		

CI, Confidence Interval; IQR, interquartile range; LSM, least squares mean; n, number of subjects who had at least one visit; N, total post baseline.
a Available data extrapolated to 12 months.

Table 14.2.3.6.8.2
Payor-Based Average Annualized Cost per Subject by Cognitive Decline

(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.8.1 for Cognitive decline (MCI due to AD vs. mild AD).

Table 14.2.3.6.8.3
Payor-Based Average Annualized Cost per Subject by CVR Score

(Intent-to-Treat)

Programming Note: For the final analysis, repeat Table 14.2.5.8.1 for CVR score (low/medium vs. high/very high).

Table 14.2.4.1.1 Exploratory Analysis of the Change from Baseline in Hippocampal Volume (Safety Population)

Use layout of 14.2.4.2.1

Table 14.2.4.1.2
Exploratory Analysis of Hippocampal Volume and Relationship with vADAS-Cog Treatment Group (Safety Population)

Hippocampal Volume vs. vADAS-Cog

	Renew NCP-5 (N=xx)			
Time Point	Hippocampal Volume		vADAS-Cog	
Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline				
n	xx		xx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx, xx		xx, xx	
Week 24				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Month 12				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Correlation coefficient		x.xxx		

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.1.3
Exploratory Analysis of Hippocampal Volume and Relationship with vADAS-Cog Active sham Group(Safety Population)

Hippocampal Volume vs. vADAS-Cog

	Active sham (N=xx)			
Time Point	Hippocampal Volume		vADAS-Cog	
Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline				
n	xx		xx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx, xx		xx, xx	
Week 24				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Month 12				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Correlation coefficient		x.xxx		

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.

Cross References: Listing 16.2.6.1.1

Programmer Note: repeat for Hippocampal Volume vs. ADCS-ADL, Hippocampal Volume vs. ADCS-CGIC (need to use frequency count and percentage summary), and Hippocampal Volume vs. ADAS-Cog14

Table 14.2.4.1.4
Exploratory Analysis of Hippocampal Volume and Relationship with ADCS-ADL Treatment Group (Safety Population)

Table 14.2.4.1.5
Exploratory Analysis of Hippocampal Volume and Relationship with ADCS-ADL Active Sham Group (Safety Population)

Table 14.2.4.1.6
Exploratory Analysis of Hippocampal Volume and Relationship with ADCS-CGIC Treatment Group (Safety Population)

Table 14.2.4.1.7
Exploratory Analysis of Hippocampal Volume and Relationship with ADCS-CGIC Active Sham Group (Safety Population)

Table 14.2.4.1.8
Exploratory Analysis of Hippocampal Volume and Relationship with ADAS-Cog14 Treatment Group (Safety Population)

Table 14.2.4.1.9
Exploratory Analysis of Hippocampal Volume and Relationship with ADAS-Cog14 Active Sham Group (Safety Population)

Table 14.2.4.2.1
Exploratory Analysis of Cerebral Blood Flow in the Hippocampus
(Safety Population)

Time Point	Renew NCP-5 (N=xx)		Active sham (N=xx)	
Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline				
n	xx		xx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx, xx		xx, xx	
Week 24				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
By visit analysis				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Month 12				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
By visit analysis				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Overall Comparison of Change from Baseline (Renew NCP-5 vs. Active sham)				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Overall p-values for Other Terms				
Baseline Value		0.xxx		

Treatment quality	0.xxx
Cognitive decline	0.xxx
CVR score	0.xxx
ApoE	0.xxx
Time point	0.xxx
Time point*Treatment	0.xxx

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Cerebral Blood Flow as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), ApoE (positive vs. negative), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.2.2
Exploratory Analysis of Cerebral Blood Flow in the Precuneus
(Safety Population)

Use layout of 14.2.4.2.1

Table 14.2.4.2.3
Exploratory Analysis of Cerebral Blood Flow in the Parietal
(Safety Population)

Use layout of 14.2.4.2.1

Table 14.2.4.2.4
Exploratory Analysis of Cerebral Blood Flow in the Inferior Frontal Lobe
(Safety Population)

Use layout of 14.2.4.2.1

Table 14.2.4.3
Exploratory Analysis of Global Cerebral Blood Flow
(Safety Population)

Use layout of 14.2.4.2.1

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Global Cerebral Blood Flow as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.4
Exploratory Analysis of White Matter Lesion Burden
(Safety Population)

Use layout of 14.2.4.2.1
There will be two tables: white matter lesion burden volume and % of total white matter volume.

Table 14.2.4.5
Exploratory Analysis of Change From Baseline on vADAScog at week 12
(Intent to Treat Population)

This analysis is described in Appendix A1 and will be a Bayesian analysis.

Change From Baseline on VADAScog at week 12	Posterior Mean	Posterior Median	Posterior Standard Deviation	Posterior 95% Credible Interval
Renew NCP-5 Arm				
Active sham Arm				
Difference Renew NCP-5 minus Active sham				
Posterior Probability Superiority of Renew NCP-5 over Active sham				

Table 14.2.4.6
Exploratory Analysis of Change From Baseline on vADAScog at week 24
(Intent to Treat Population)

This analysis is described in Appendix A1 and will be a Bayesian analysis.

Change From Baseline on vADAScog at week 24	Posterior Mean	Posterior Median	Posterior Standard Deviation	Posterior 95% Credible Interval
Renew NCP-5 Arm				
Active sham Arm				
Difference Renew NCP-5 minus Active sham				

Posterior Probability Superiority of Renew NCP-5 over Active sham	

Table 14.2.4.7
Exploratory Analysis of Deep Tissue Oxygenation and Blood Viscosity
(Safety Population)

Use layout of 14.2.4.2.1, separate "Deep Tissue Oxygenation" from "Blood Viscosity"

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Deep Tissue Oxygenation and Blood Viscosity as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.8
Exploratory Analysis of Lipid Panel: Total Cholesterol, LDL-C, HDL-C, Triglycerides, Blood Fibrinogen
(Safety Population)

Use layout of 14.2.4.2.1, separate "Total Cholesterol", "LDL-C", "HDL-C", "Triglycerides", "Blood Fibrinogen"

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Lipid Panel: Total Cholesterol, LDL-C, HDL-C, Triglycerides, Blood Fibrinogen as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix

including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.9
Exploratory Analysis of Inflammatory Markers: C-Reactive Protein (CRP), Lp-PLA2 and MPOS (Safety Population)

Use layout of 14.2.4.2.1, separate "C-Reactive Protein (CRP)", "Lp-PLA2" "MPOS"

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Inflammatory Markers: C-Reactive Protein (CRP), Lp-PLA2 and MPOS as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.10
Exploratory Analysis of CBC: Including Red Cell Distribution Width (RDW) and Hemoglobin (Safety Population)

Use layout of 14.2.4.2.1, separate "Red Cell Distribution Width (RDW)" from "Hemoglobin"

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in CBC: Including Red Cell Distribution Width (RDW) and Hemoglobin as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.11
Exploratory Analysis of Polymorphism of the Apolipoprotein Gene and its Effect in Modulating Hippocampal Changes (Safety Population)

Time Point	Renew NCP-5 (N=xx)		Active sham (N=xx)	
Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline				
n	xx		xx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx, xx		xx, xx	
Week 24				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
By visit analysis				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Month 12				
n	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
By visit analysis				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Overall Comparison of Change from Baseline (Renew NCP-5 vs. Active sham)				
LS Mean (SE)		xx.xx (x.xxx)		xx.xx (x.xxx)
Difference in LS Mean (SE)		xx.xx (x.xxx)		
95% Confidence Interval for Difference		(xx.xx, xx.xx)		
p-value		0.xxx		
Overall p-values for Other Terms				
Baseline Value		0.xxx		

Treatment quality	0.xxx
Cognitive decline	0.xxx
CVR score	0.xxx
ApoE	0.xxx
Time point	0.xxx
Time point*Treatment	0.xxx

Abbreviations: ApoE = Polymorphism of the Apolipoprotein, Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Hippocampal Changes as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), ApoE (positive, negative), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.12
Exploratory Analysis of Behavioral Assessment Measured via NPI Aggression Index Score (Safety Population)

Use layout of 14.2.4.2.1

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Behavioral Assessment as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.13
Exploratory Analysis of Balance, Functional Mobility, and Fall-Risk Assessment Measured via Time Up and Go Test (TUG) and the Functional Reach Test (Safety Population)

Use layout of 14.2.4.2.1

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in Balance, Functional Mobility, and Fall-Risk Assessment as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.14.1
Exploratory Analysis of ADAS Delayed Word Recall and ADAS Word Recognition (a sub-test of the vADAS cog)

(Intent-to-Treat Population)

Use layout of 14.2.4.2.1, separate "ADAS Delayed Word Recall" from "ADAS Word Recognition"

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
Note: Baseline value is defined as the last measurement taken prior to first treatment in the study.
Note: Change from baseline in ADAS Delayed Word Recall and ADAS Word Recognition as a continuous variable is based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline value, treatment quality, cognitive decline (MCI due to AD, mild AD), CVR score (Low/Medium Risk, High/Very High Risk), treatment group, time point, and interaction of timepoint and treatment.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.14.2
Exploratory Analysis of ADAS Delayed Word Recall and ADAS Word Recognition (a sub-test of the vADAS cog)
(Per-Protocol Population)

Table 14.2.4.14.3
Exploratory Analysis of ADAS Delayed Word Recall and ADAS Word Recognition (a sub-test of the vADAS cog) Excluding the Data from Subjects Impacted by COVID-19
(Intent-to-Treat Population)

Table 14.2.4.14.4
Exploratory Analysis of ADAS Delayed Word Recall and ADAS Word Recognition (a sub-test of the vADAS cog) Subgroup by Cognitive Decline
(Intent-to-Treat Population)

Table 14.2.4.14.5
Exploratory Analysis of ADAS Delayed Word Recall and ADAS Word Recognition (a sub-test of the vADAS cog) Subgroup by CVR Score
(Intent-to-Treat Population)

Table 14.2.4.15.1
Exploratory Analysis of Digital Twin Data using ADAS-Cog12: ITT (Intent-to-Treat Population)

Time Point	Statistics	Paired Differences (Treatment vs Digital Twins)	Paired Differences (Active sham vs Digital Twins)
12 weeks	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
	Estimated ATE (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
	95% CI for ATE	(xx.xx, xx.xx)	(xx.xx, xx.xx)
	P-value for ATE	0.xxx	0.xxx
	P-value for CVR	0.xxx	0.xxx
	P-value for disease stage	0.xxx	0.xxx
24 weeks	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
	Estimated ATE (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
	95% CI for ATE	(xx.xx, xx.xx)	(xx.xx, xx.xx)
	P-value for ATE	0.xxx	0.xxx

	P-value for CVR	0.xxx	0.xxx
	P-value for disease stage	0.xxx	0.xxx
9 months	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
	Estimated ATE (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
	95% CI for ATE	(xx.xx, xx.xx)	(xx.xx, xx.xx)
	P-value for ATE	0.xxx	0.xxx
	P-value for CVR	0.xxx	0.xxx
	P-value for disease stage	0.xxx	0.xxx
12 months	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
	Estimated ATE (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
	95% CI for ATE	(xx.xx, xx.xx)	(xx.xx, xx.xx)
	P-value for ATE	0.xxx	0.xxx
	P-value for CVR	0.xxx	0.xxx
	P-value for disease stage	0.xxx	0.xxx

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation, ATE = Average treatment effect, SE = standard error, CI = Confidence interval."

Table 14.2.4.15.2
Exploratory Analysis of Digital Twin Data using ADAS-Cog12: Per Protocol (Per Protocol Population)

This table should look identical to Table 14.2.4.15.1, except that "Intent-to-Treat Population" should be replaced by "Per Protocol Population".

Table 14.2.4.16.1
Exploratory Analysis of Proportion of Subjects with vADAS Responders
(Intent-To-Treat Population)

Time Point Parameter	Renew NCP-5 (N=XX)	Active sham (N=XX)
Week 12		
Responders, n (%)	xx (xx.x)	xx (xx.x)
95% Confidence Interval [1]	xx.x, xx.x	xx.x, xx.x
CMH Test Proportion Difference [2]	xx.x	
95% Confidence Interval [2]	xx.x, xx.x	
p-value [2]	0.xxx	
Week 18		
Responders, n (%)	xx (xx.x)	xx (xx.x)
95% Confidence Interval [1]	xx.x, xx.x	xx.x, xx.x
CMH Test Proportion Difference [2]	xx.x	
95% Confidence Interval [2]	xx.x, xx.x	
p-value [2]	0.xxx	
Repeat for Week 24, etc.		

Abbreviations: CMH = Cochran-Mantel-Haenszel.
[1] Two-sided 95% Exact (Clopper-Pearson) confidence interval.
[2] The stratified difference is a weighted average of the difference within each stratum. Estimates from the strata cognitive decline (MCI due to AD, mild AD), CVR score (low/medium, high/very high), and ApoE (positive vs. negative), are combined with CMH weights. The estimate and confidence interval are expressed as percentages.

Cross References: Listing 16.2.6.1.1

Table 14.2.4.16.2
Exploratory Analysis of Proportion of Subjects with vADAS Responders
(Per-Protocol Population)

Table 14.2.4.16.3
Exploratory Analysis of Proportion of Subjects with vADAS Responders Excluding the Data from Subjects Impacted by COVID-19 (Intent-To-Treat Population)

Table 14.2.4.16.4
Exploratory Analysis of Proportion of Subjects with vADAS Responders Subgroup by Cognitive Decline (Intent-To-Treat Population)

USING CHI-SQUARE TEST

Table 14.2.4.16.5
Exploratory Analysis of Proportion of Subjects with vADAS Responders Subgroup by CVR Score (Intent-To-Treat Population)

USING CHI-SQUARE TEST

Table 14.2.4.17.1
Exploratory Analysis of the Average of the Change from Baseline in vADAS-Cog Score (Intent-To-Treat Population)

USE LAYOUT OF 14.2.2.2.1

Table 14.2.4.17.2
Exploratory Analysis of the Average of the Change from Baseline in vADAS-Cog Score (Per-Protocol Population)

USE LAYOUT OF 14.2.2.2.1

Table 14.2.4.17.3
Exploratory Analysis of the Average of the Change from Baseline in vADAS-Cog Score Excluding the Data from Subjects Impacted by COVID-19 (Intent-To-Treat Population)

USE LAYOUT OF 14.2.2.2.1

Table 14.2.4.17.4
Exploratory Analysis of the Average of the Change from Baseline in vADAS-Cog Score Subgroup by Cognitive Decline (Intent-To-Treat Population)

Table 14.2.4.17.5
Exploratory Analysis of the Average of the Change from Baseline in vADAS-Cog Score Subgroup by CVR Score (Intent-To-Treat Population)

Table 14.2.4.17.6 Exploratory Analysis of the Average of the Change from Baseline in vADAS-Cog Score Subgroup by Significant Comorbidities (Intent-To-Treat Population)

USE LAYOUT OF 14.2.2.2.1
Individual tables for each sub-group: diabetes, sleep disorders, mental health disorders, and thyroid disorders

Table 14.2.4.17.7
Exploratory Analysis of the Average of the Change from Baseline in vADAS-Cog Score Subgroup by Significant Concurrent Medications (Intent-To-Treat Population)

USE LAYOUT OF 14.2.2.2.1
Individual tables for each sub-group: thyroid, sedation, cognition/memory, and antidepressants/anti-anxiety medications

Table14.2.4.18.1
Exploratory Analysis of ADCS-CGIC Follow-up
(Intent-To-Treat Population)

Use layout of Table 14.2.2.1.1

Table14.2.4.18.2
Exploratory Analysis of ADCS-CGIC Follow-up
(Per-Protocol Population)

Use layout of Table 14.2.2.1.1

Table14.2.4.18.3
Exploratory Analysis of ADCS-CGIC Follow-up: Excluding the Data from Subjects Impacted by COVID-19
(Intent-To-Treat Population)

Use layout of Table 14.2.2.1.1

Table14.2.4.18.4
Exploratory Analysis of ADCS-CGIC Follow-up: Subgroup by Cognitive Decline
(Intent-To-Treat Population)

Use layout of Table 14.2.2.1.1

Table14.2.4.18.5
Exploratory Analysis of ADCS-CGIC Follow-up: Subgroup by CVR Score
(Intent-To-Treat Population)

Use layout of Table 14.2.2.1.1

Table14.2.4.19.1
Exploratory Analysis of Executive Function Assessed by Trail Making Test B Follow-up
(Intent-To-Treat Population)

Use layout of Table 14.2.3.1.1

Table14.2.4.19.2
Exploratory Analysis of Executive Function Assessed by Trail Making Test B Follow-up
(Per-Protocol Population)

Use layout of Table 14.2.3.1.1

Table14.2.4.19.3
Exploratory Analysis of Executive Function Assessed by Trail Making Test B Follow-up: Excluding the Data from Subjects Impacted by COVID-19
(Intent-To-Treat Population)

Use layout of Table 14.2.3.1.1

Table14.2.4.19.4
Exploratory Analysis of Executive Function Assessed by Trail Making Test B Follow-up: Subgroup by Cognitive Decline
(Intent-To-Treat Population)

Use layout of Table 14.2.3.1.1

Table14.2.4.19.5
Exploratory Analysis of Executive Function Assessed by Trail Making Test B Follow-up: Subgroup by CVR Score
(Intent-To-Treat Population)

Use layout of Table 14.2.3.1.1

Table14.2.4.20.1
Exploratory Analysis of ADAS-Cog14 Follow-up
(Intent-To-Treat Population)

Use layout of Table 14.2.3.1.1

Table14.2.4.20.2
Exploratory Analysis of ADAS-Cog14 Follow-up
(Per-Protocol Population)

Use layout of Table 14.2.3.1.1

Table14.2.4.20.3
Exploratory Analysis of ADAS-Cog14 Follow-up: Excluding the Data from Subjects Impacted by COVID-19 (Intent-To-Treat Population)
Use layout of Table 14.2.3.1.1

Table14.2.4.20.4
Exploratory Analysis of ADAS-Cog14 Follow-up: Subgroup by Cognitive Decline (Intent-To-Treat Population)
Use layout of Table 14.2.3.1.1

Table14.2.4.20.5
Exploratory Analysis of ADAS-Cog14 Follow-up: Subgroup by CVR Score (Intent-To-Treat Population)
Use layout of Table 14.2.3.1.1

Table14.2.4.21.1
Exploratory Analysis of the Average of the Change from Baseline in ADCS-ADL at 12, 18 and 24 weeks after Initiation of Treatment (Intent-To-Treat Population)
Use layout of 14.2.2.2.1

Table14.2.4.21.2
Exploratory Analysis of the Average of the Change from Baseline in ADCS-ADL at 12, 18 and 24 weeks after Initiation of Treatment (Per Protocol Population)
Use layout of 14.2.2.2.1

Table14.2.4.21.3
Exploratory Analysis of the Average of the Change from Baseline in ADCS-ADL at 12, 18 and 24 weeks after Initiation of Treatment: Excluding the Data from Subjects Impacted by COVID-19
(Intent-To-Treat Population)

Use layout of 14.2.2.2.1

Table14.2.4.21.4
Exploratory Analysis of the Average of the Change from Baseline in ADCS-ADL at 12, 18 and 24 weeks after Initiation of Treatment: Subgroup by Cognitive Decline
(Intent-To-Treat Population)

Use layout of 14.2.2.2.1

Table14.2.4.21.5
Exploratory Analysis of the Average of the Change from Baseline in ADCS-ADL at 12, 18 and 24 weeks after Initiation of Treatment: Subgroup by CVR Score
(Intent-To-Treat Population)

Use layout of 14.2.2.2.1

Table 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
(Safety Population)

	Renew NCP-5 N=xx n (%): Events	Active sham N=xx n (%): Events
Any TEAEs	xx (xx.x): xx	xx (xx.x): xx
Any Serious TEAEs	xx (xx.x): xx	xx (xx.x): xx
Any TEAEs Related to Treatment	xx (xx.x): xx	xx (xx.x): xx
Any Serious TEAEs Related to Treatment	xx (xx.x): xx	xx (xx.x): xx
Any TEAEs Leading to Withdrawal of Treatment	xx (xx.x): xx	xx (xx.x): xx
Any TEAEs Leading to Death	xx (xx.x): xx	xx (xx.x): xx

Abbreviations: TEAEs = Treatment Emergent Adverse Events.
Note: Percentages are based on the number of subjects in the Safety population. TEAEs are defined as events with an onset date on or after the first treatment.

Cross References: Listing 16.2.7.1

Table 14.3.1.2
Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Renew NCP-5 (N=xx) n (%)	Active sham (N=xx) n (%)
Any TEAEs	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
…		
System Organ Class 2	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
…		

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, TEAEs = Treatment Emergent Adverse Events.
Note: Percentages are based on the number of subjects in the safety population. Adverse events are coded using MedDRA version 22.0. At each level of summarization, subjects who experienced more than one event are counted only once. Events are sorted alphabetically by system organ class and by preferred term within system organ class. TEAEs are defined as events with an onset date on or after the first treatment.

Cross References: Listing 16.2.7.1

Table 14.3.1.3
Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Safety Population)

System Organ Class Preferred Term Severity	Renew NCP-5 (N=xx) n (%)	Active sham (N=xx) n (%)
Any TEAEs	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)
Mild	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)
Mild	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)
Mild	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
…		

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, TEAEs = Treatment Emergent Adverse Events.
Note: Percentages are based on the number of safety population in each treatment group. Adverse events are coded using MedDRA version 22.0. A subject is counted once for each system organ class (SOC) at the maximum severity level reported for that SOC and once for each unique preferred term (PT) within that SOC level at the maximum severity level reported for that PT. Events are sorted alphabetically by system organ class and by preferred term within system organ class. Treatment-emergent AEs (TEAEs) are defined as events with an onset date and time on or after the first treatment.

Cross References: Listing 16.2.7.1

Table 14.3.1.4
Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Treatment (Safety Population)

System Organ Class Preferred Term Relationship	Renew NCP-5 (N=xx) n (%)	Active sham (N=xx) n (%)
Any TEAEs	xx (xx.x)	xx (xx.x)
Probably related	xx (xx.x)	xx (xx.x)
Suspected	xx (xx.x)	xx (xx.x)
Not related	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)
Probably related	xx (xx.x)	xx (xx.x)
Suspected	xx (xx.x)	xx (xx.x)
Not related	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Probably related	xx (xx.x)	xx (xx.x)
Suspected	xx (xx.x)	xx (xx.x)
Not related	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
…		

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, TEAEs = Treatment Emergent Adverse Events.
Note: Percentages are based on the number of safety population in each treatment group. Adverse events are coded using MedDRA version 22.0. A subject is counted once for each system organ class (SOC) at the most relationship level reported for that SOC and once for each unique preferred term (PT) within that SOC level at the maximum severity level reported for that PT. Events are sorted alphabetically by system organ class and by preferred term within system organ class. Treatment-emergent AEs (TEAEs) are defined as events with an onset date and time on or after the first treatment.

Cross References: Listing 16.2.7.1

Table 14.3.1.5
Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

Use layout of 14.3.1.2
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, TEAEs = Treatment Emergent Adverse Events.
Note: Percentages are based on the number of subjects in the safety population. Adverse events are coded using MedDRA version 22.0. At each level of summarization, subjects who experienced more than one event are counted only once. Events are sorted alphabetically by system organ class and by preferred term within system organ class. TEAEs are defined as events with an onset date on or after the first treatment.

Cross References: Listing 16.2.7.1

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Population)

Use layout of 14.3.1.2
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, TEAEs = Treatment Emergent Adverse Events.
Note: Percentages are based on the number of subjects in the safety population. Adverse events are coded using MedDRA version 22.0. At each level of summarization, subjects who experienced more than one event are counted only once. Events are sorted alphabetically by system organ class and by preferred term within system organ class. TEAEs are defined as events with an onset date on or after the first treatment.

Cross References: Listing 16.2.7.1

Table 14.3.4.1
Summary and Change from Baseline in Hematology Laboratory Test Results
(Safety Population)

Parameter: Parameter Name (unit)

	Renew NCP-5 (N=xx)		Active sham (N=xx)	
Visit Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline [1]				
n	xx		xx	
Mean (SD)	xx.xx (xx.xxx)		xx.xx (xx.xxx)	
Median	xx.xx		xx.xx	
Min, Max	xx.x, xx.x		xx.x, xx.x	
Week 12				
n	xx	xx	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.xx	xx.xx	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 24				
n	xx	xx	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.xx	xx.xx	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Etc.				

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
[1] Baseline is defined as the last measurement taken prior to first treatment.

Cross References: Listing 16.2.8.1.1

Programming Note: Sort the parameters in the order that they appear on the lab report. Continue for visit Month 12.

Table 14.3.4.2
Summary and Change from Baseline in Chemistry Laboratory Test Results
(Safety Population)

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
[1] Baseline is defined as the last measurement taken prior to first treatment.

Cross References: Listing 16.2.8.2

Programming Note: Sort the parameters in the order that they appear on the lab report. Continue for visit Month 12.

Table 14.3.4.3
Hematology Laboratory Test Results Shift from Baseline (Safety Population)

Parameter: Parameter Name (unit)

	Baseline [1]							
	Renew NCP-5 N=XX				Active sham N=XX			
Visit Result	Low n (%)	Normal n (%)	High n (%)	Total n (%)	Low n (%)	Normal n (%)	High n (%)	Total n (%)
Week 12								
Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100)
Week 24								
Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100)
Month 12								
Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100)

Note: If multiple assessments occur at a given post-baseline time point, the latest value is used in the summary. Percentages are based on the number of subjects with non-missing values at the given visit and baseline in the Safety Population in each treatment group.
[1] Baseline is defined as the last measurement taken prior to first treatment.

Cross References: Listing 16.2.8.1.1

Programming Note: Sort the parameters in the order that they appear on the lab report.

Table 14.3.4.4
Chemistry Laboratory Test Results Shift from Baseline
(Safety Population)

Note: If multiple assessments occur at a given post-baseline time point, the latest value is used in the summary. Percentages are based on the number of subjects with non-missing values at the given visit and baseline in the Safety Population in each treatment group.
[1] Baseline is defined as the last measurement taken prior to first treatment.

Cross References: Listing 16.2.8.2

Programming Note: Sort the parameters in the order that they appear on the lab report.

Table 14.3.4.5
Summary and Change from Baseline in Vital Signs
(Safety Population)

Parameter: Parameter Name (unit)

	Renew NCP-5 (N=xx)		Active sham (N=xx)	
Visit Statistics	Observed	Change from Baseline	Observed	Change from Baseline
Baseline [1]				
n	xx		xx	
Mean (SD)	xx.xx (xx.xxx)		xx.xx (xx.xxx)	
Median	xx.xx		xx.xx	
Min, Max	xx.x, xx.x		xx.x, xx.x	
Visit #2				
n	xx	xx	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.xx	xx.xx	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Visit #2				
n	xx	xx	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.xx	xx.xx	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Etc.				

Abbreviations: Max = Maximum, Min = Minimum, SD = Standard Deviation.
[1] Baseline is defined as the last measurement taken prior to first treatment.

Cross References: Listing 16.2.9.1

APPENDIX C: Health Resource Utilization (HRU) Analysis Plan

1. INTRODUCTION

The HRU collected at study initiation included medications and procedures only. Since there are insufficient electronic medical records (EMR) available to capture HRU retrospectively; additional HRU was collected using the Alzheimer's disease Cooperative Study (ADCS) Resource Use Inventory (RUI), a patient-reported outcome (PRO). The RUI was introduced to the study in December 2019, after enrollment for the study commenced on December 2018. Subjects participate in the study for up to 13 months (up to 28 days screening, 24 weeks treatment and 6 months follow-up).

This supplementary Statistical Analysis Plan (SAP) complements the main study SAP detailing the HRU specific analyses.

1.1 Health Resource Use Objectives

The objectives of this supplementary analysis is to compare the direct HRU and related costs, attributable to payers, between the Renew™ NCP-5 treatment group and active sham group.

1.2 Study design

This study is a multi-center, prospective, randomized, trial of Renew™ NCP-5 in patients with mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's dementia. A minimum of 100 and a maximum of 250 patients will be enrolled. Patients will be randomized 1:1 to either Renew™ NCP-5 (treatment) or active sham (control). This trial will have frequent interim analyses to stop enrollment for expected success or to stop for futility.

Subjects, ages 55-85, will be consented for 13 months and will receive thirty-five 60-minute Renew™ NCP-5 treatment sessions during a 7-to-12-week initial treatment period, and then transition to a lower frequency maintenance period (twice a week) for a total treatment period of 24 weeks. During the initial treatment period (~1-12 weeks) subjects should be treated five days per week but at a minimum receive treatments three days per week. In addition to laboratory assessments to support the exploratory analyses of the main study, subjects will undergo testing sessions for secondary psychological assessments completed by blinded psychometricians.

In addition to the main study psychometric assessments, the RUI will be provided to patients within the NCP-5-1001 study to capture direct medical and non-medical HRU at baseline, 3, 6, 9 and 12 months. Given, the study enrollment status, RUI will not be collected for many subjects at baseline and 3 months, however the majority of subjects will complete the RUI at 6, 9 and 12 months, depending on their enrollment date. This ASCS developed and validated instrument was not part of the initial study materials, but was included in December 2019. There are no other modifications to the main study design.

1.2.1 Data source(s)

The RUI is a validated measure of HRU capturing direct medical HRU along with informal care resources developed as part of the Alzheimer's disease Cooperative Study (ADCS) instrument development program. It uses a 3-month recall period which affords the possibility for 12 months of complete HRU for some patients, with the majority having 9 months HRU post-randomization. The RUI was designed to be completed by subjects and/or caregivers with little or no assistance from site staff.[2] The RUI was designed for healthy elderly subjects as they begin to demonstrate cognitive deterioration, but has also been successfully applied to subjects with mild cognitive impairment.[3]

Only 5 of the 9 items which make up the RUI will be collected including: inpatient care, emergency room visits, health care professional visits, durable medical equipment, overnight care, and home health aide (items 1, 2, 3, 5, 6 respectively, as highlighted in Exhibit 1 below). Medical tests and procedures are currently being collected in the Renew™ NCP-5 study, and therefore RUI item 4 can be excluded. The informal care and subject's time use domains of the RUI (items 7, 8 and 9) are not required.

Exhibit 1. Summary of Resource Use Instrument Items Required

Domain	RUI Item	HRU to collect	Currently Collected	Collection Required
Direct medical care	1	Inpatient	No	Yes
	2	Health Care Professional / ER	No	Yes
	3	Durable medical equipment	No	Yes
	4	Outpatient medical tests and procedures	Yes	No
	NA	Medications	Yes	No
Direct nonmedical	5	Overnight Care (excluding inpatient)	No	Yes
	6	Home health aid	No	Yes
Informal care	7, 8	Informal care hours	No	No
Subject's time use	9	Employment / Volunteer	No	No

2. ANALYSIS SETS

2.1 Intention-to-treat (ITT) population

The ITT population will be used for these supplementary HRU analyses, and will consist of all subjects who are enrolled and randomized into either active treatment group or active sham group.

2.2 Subgroups

Analyses will be conducted among the following subgroups:

[2] Sano M, Zhu CW, Whitehouse PJ, et al. ADCS Prevention Instrument Project: pharmacoeconomics: assessing health-related resource use among healthy elderly. *Alzheimer Dis Assoc Disord*. 2006;20(4 Suppl 3):S191–S202.
[3] Zhu CW, Sano M, Ferris SH, Whitehouse PJ, Patterson MB, Aisen PS. Health-related resource use and costs in elderly adults with and without mild cognitive impairment. J Am Geriatr Soc 2013;61:396–402.

- Cognitive decline (MCI due to AD vs. mild AD)
- Cerebrovascular reactivity (CVR) score (low/medium vs. high/very high)

3. OUTCOMES

The following HRU outcomes and associated payer costs will be assessed as part of this supplementary SAP:

Direct Medical

- Number and annual rate of hospital admissions
    - Reason for admission
    - Number of nights
- Number and annual rate of outpatient clinician visits
- Durable medical equipment usage

Direct Non-medical

- Number of nights spent in "overnight care" per annum
- Number of hours of home health aide, attendant, companion, or other paid individual care per annum

Further, overall annual HRU payer costs associated with medications in addition to aforementioned outcomes will be provided.

4. ANALYTIC METHODS

Analyses will be performed using SAS Software, Version 9.4 or higher (SAS Institute, Cary, North Carolina). Table shells of the analysis are provided below.

4.1 Statistical Methods

Descriptive summary statistics for continuous variables will include the number of subjects (n), mean, standard deviation (SD), median, interquartile range (IQR), and range.

Descriptive summary statistics for categorical variables will include frequency counts and percentages [n (%)]. Unless stated otherwise in the table shells, the denominator for percentage calculations will be the number of subjects in the analysis population. The category "Missing" will be presented if the number missing is greater than zero for at least one treatment group. The percentage and continuous summary statistics, when relevant, will be suppressed when the count is zero.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, and confidence intervals (CIs) will be displayed to one level of precision greater than the data collected. Standard deviation and incidence rate ratios (IRR) will be displayed to two levels of precision greater than the data collected. p-

values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." All significance tests will be two-sided and use a 5% significance level.

4.1.1 Healthcare Resource Utilization

The annual rate of HRU will be reported and compared between the Renew™ NCP-5 treatment and active sham groups using a Poisson model. The Poisson model assumes that each HRU event does not influence the probability that a subsequent HRU event will occur. Scale parameters may be specified in the models in cases where adjustment for over-dispersion is necessary (i.e., when the variance is larger than the mean). Another model, such as the negative binomial, may be considered if there are a lot of patients without that HRU event. The period over which HRU is measured will vary between patients due to the late implementation of HRU collection. An offset will be included in the Poisson model to adjust for variable HRU collection period.

4.1.2 Payer Costs

The mean payer costs related to the HRU will reported and compared between the Renew™ NCP-5 treatment and active sham groups using a generalized linear model with gamma distribution and log link, for instance. Cost data is generally highly skewed and therefore bootstrapping may be employed to provide accurate confidence intervals of the mean cost within and between groups.
Payer costs for all health resources used by patients will be estimated based on the reimbursement amount for each encounter, and will assessed using Medicare standard payment rates for the appropriate setting of care.

Specifically, for:

- Medications: the unit costs will be evaluated using Medicare's average sales price rates from the most recent quarterly data available.

- Inpatient stays: costs for services will be estimated using the average reimbursement diagnosis-related group (DRG) amounts per stay for subjects with a primary diagnosis of mild cognitive impairment. The average reimbursement amount will be evaluated using the 5% sample Standard Analytic Files (SAFs) from claims processed in 2019.

- Outpatient clinician visits: costs for physician services provided will be estimated using the Medicare average national reimbursement per visit for subjects with a primary diagnosis of mild cognitive impairment (International Classification of Disease, Tenth Revision, Clinical Modification [ICD-10-CM: G31.84]). The average reimbursement amount will be evaluated using the 5% sample SAFs from claims processed in 2019, or alternatively using the Medicare reimbursement for an evaluation and management visit for an established patient (Current Procedural Terminology [CPT] 99214) and CPT 97110 for physical therapy visits. If the total

number of visits is greater than the sum of individual visits, the difference in visits will be treated as Doctor visits and costed as General Practitioner visits. Otherwise, specific visit counts reported will be used.

- Emergency room visits: costs will be estimated using the average reimbursement Ambulatory Payment Classification (APC) group[4] amounts per visit for subjects with a primary diagnosis of mild cognitive impairment. The reimbursement rate will be evaluated from the Hospital Outpatient Prospective Payment System file from claims processed in 2019.

- Durable medical equipment: costs will be assessed from the Medicare fee schedule[5]

- Assisted living care, nursing home care, and respite: costs will be estimated from Genworth[6]. The median daily rate will be used if at least 44 hours of care per week on average was reported. Otherwise, the median hourly rate will be used. If days is reported and hours is not provided within the RUI, then the mean daily rate will be used for costing, and 8 hours will be included in HRU summaries.

All costs will be reflected in 2020 United States (US) dollars.

4.1.3 Handling of dropouts or missing data

Only available data will be summarized; no imputation of missing data will be conducted as part of the supplementary HRU analyses, but any imputations provided within the main study data will also be utilized for these analyses, as relevant. HRU and HRU cost data will be annualized. Sensitivity analyses of HRU costs may be conducted excluding subject visit information if the implemented RUI questions for that visit are partially missing.

4.2 Analysis

4.2.1 RUI Completion Status

The n (%) of subjects who were provided the RUI, and the n (%) who subsequently provided a response on or completed the RUI for each study visit will be summarized. The total RUI follow-up time, post baseline will also be summarized. (Table 14.2.5.1)

[4] Centers for Medicare & Medicaid Services. Medicare Hospital Outpatient Prospective Payment System.
[5] Center for Medicare & Medicaid Services. DMEPOS fee schedule. Available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/DMEPOSFeeSched/DMEPOS-Fee-Schedule.html. Accessed October 2, 2019.
[6] Genworth Cost of Care Survey [online]. Available at: https://www.genworth.com/about-us/industry-expertise/cost-of-care.html. Accessed October 2, 2019.

4.2.2 Healthcare Resource Utilization

The total HRU captured for each subject will be extrapolated to provide annualized results. With the exception of durable medical equipment, HRU will also be summarized overall and by treatment group for each visit. Standard descriptive statistics will be presented for the categorical and continuous variables, and comparisons of HRU between treatment groups will be assessed with IRR (95% CI) and corresponding p-value for inpatient stays (Table 14.2.5.2*), outpatient clinician visits (Appendix I, Table 3), durable medical equipment (Table 14.2.5.4*), overnight care (Table 14.2.5.5*), and paid individual care (Table 14.2.5.6*). HRU will also be presented by cognitive decline (MCI due to AD vs. mild AD) and CVR score (low/medium vs. high/very high) subgroups for the final analyses.

4.2.3 Payer Costs

Unit costs for all HRU will be detailed (Table 14.2.5.7), and used to determine costs of care by multiplying the number of resource units used by the corresponding unit cost per individual. Annualized costs for prescription medications, inpatient stays, outpatient clinician visits, durable medical equipment, overnight care, and paid individual care will be summarized along with total direct medical, non-medical, and overall costs (Table 14.2.5.8*). Costs will be compared between treatment groups with LSM differences and corresponding p-values. HRU costs will also be presented by cognitive decline (MCI due to AD vs. mild AD) and CVR score (low/medium vs. high/very high) subgroups for the final analyses.

4.3 Interim analysis

For the main study, interim analyses will be conducted based on the number of subjects who have randomized into the trial and will begin when 100 patients have been randomized with subsequent interim analyses conducted after every additional 25 subjects. The HRU supplementary analyses will be conducted as part of the final analysis. If produced as part of an interim analysis only the overall tables will be produced. Assuming at least 25 subjects per sub-group, sub-group analyses by cognitive decline (MCI due to AD vs. mild AD) and CVR score (low/medium vs. high/very high) will also be conducted for the final analyses.

4.4 Changes in planned analyses

These analyses will be performed in addition to all main study SAP analyses in order to supplement HRU information.

5. ANALYSIS TABLE SHELLS

See Appendix B2.

APPENDIX D: Investigator Brochure

This will be supplied as a separate attachment to sites.

APPENDIX E: Training Manual

This will be supplied as a separate attachment to sites.

APPENDIX F: Device Inspection Checklist

This will be supplied as a separate attachment to sites.