STATISTICAL ANALYSIS PLAN

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACODYNAMICS OF CVL-871 IN SUBJECTS WITH DEMENTIA-RELATED APATHY

Compound: Razpipadon (ABBV-1871)

Trial Phase: 2a

Short Title: A Trial of the Safety, Tolerability, and Pharmacodynamics of CVL-871 in Subjects With Dementia-Related Apathy

Sponsor Name: Cerevel Therapeutics, LLC

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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Prepared by:

[redacted] *Electronically signed by: [redacted] Reason: Prepared By* [redacted] [redacted]

[redacted]
PPD

Date

[redacted] *Electronically signed by: [redacted] Reason: Prepared By* [redacted] [redacted]

[redacted]
AbbVie, Inc.

Date

Approved by:

[redacted] *Electronically signed by: [redacted] Reason: Approver* [redacted] [redacted]

[redacted]
AbbVie, Inc.

Date

Approved by:

[redacted]

Electronically signed by: [redacted]
Reason: Approver
[redacted]

[redacted]

Date

[redacted]
AbbVie, Inc.

[redacted]

Electronically signed by: [redacted]
Reason: Approver
[redacted]

[redacted]

Date

[redacted]
AbbVie, Inc.

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1. INTRODUCTION

This document provides the detailed statistical methodology for the analysis of data gathered for the Cerevel Therapeutics Study CVL-871-2001. The table, listing and figure shells supporting the Statistical Analysis Plan (SAP) can be found in a separate SAP shell document.

The analyses described herein are based on the Clinical Study Protocol (CSP) amendment Version 4.0, dated 14 February 2023. In November 2024, the sponsor made a decision to close enrollment of this exploratory study. This decision is not associated with any safety concerns. The SAP has, therefore, been revised to reflect the adjusted scope of analyses applicable to available data. Any changes or revisions to the planned analysis described in this document have been made prior to database lock.

Background information is provided for the study designs and objectives. Further details of study conduct, and data collection are provided in the study protocol and electronic case report forms (eCRFs).

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are shown in Table 1.

Table 1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To assess the safety and tolerability of 2 fixed doses of CVL-871 in subjects with dementia-related apathy	• Incidence and severity of TEAEs • Clinically significant changes in ECG results, clinical laboratory evaluations, vital sign measurements, and physical and neurological examination results • Clinically significant findings in suicidality assessed using the C-SSRS
Secondary	
• To assess the pharmacodynamic effects of 2 fixed doses of CVL-871 on apathy in subjects with dementia-related apathy	• Change from baseline to Visit 5 (Week 6) and Visit 6 (Week 12) in the following: o NPI-C apathy domain score o NPI apathy domain score o DAIR score o AES-C score
Exploratory	
• To evaluate the plasma concentrations of CVL-871 in subjects with dementia-related apathy	• Plasma concentrations of CVL-871 at Visits 2 (Week 1), 4 (Week 3), 5 (Week 6), and 6 (Week 12)
• To evaluate the effect of CVL-871 neuropsychiatric symptoms other than apathy	• NPI-C dysphoria domain score • NPI domain scores (other than apathy)
• To assess the effects of 2 fixed doses of CVL-871 on cognition in subjects with dementia-related apathy	• Change from baseline to Visit 6 (Week 12) in the ADAS-Cog13 score
• To assess the effects of 2 fixed doses of CVL-871 on functional assessments (eg, activities of basic living, and cognitive, functional, and behavioral performance) in subjects with dementia-related apathy	• Change from baseline to Visit 5 (Week 6) and Visit 6 (Week 12) in the following: o mADCS-CGIC scores o mCGI-S scores o CaGI-S scores o CaGI-C scores
• Investigate the impact of COMT (Val-Met) status on safety and pharmacodynamics	• Evaluation of safety and pharmacodynamic endpoints in subgroups of subjects based on their COMT (Val-Met) status

Abbreviations: ADAS-Cog13=Alzheimer's Disease Assessment Scale – Cognition 13-item scale; AES-C=Apathy Evaluation Scale-Clinician; COMT=catechol-O-methyltransferase; C-SSRS=Columbia-Suicide Severity Rating Scale; DAIR=Dementia Apathy Interview and Rating; ECG=electrocardiogram; mADCS-CGIC=modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; CaGI-C=Caregiver Global Impression–Change Scale; CaGI-S=Caregiver Global Impression–Severity Scale; mCGI-S=modified Clinical Global Impression–Severity Scale; NPI=Neuropsychiatric Inventory; NPI-C=Neuropsychiatric Inventory -Clinician; TEAE=treatment-emergent adverse event.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial with a 12-week treatment period to evaluate the safety, tolerability, and pharmacodynamics of 2 fixed doses of CVL-871 (1.0 mg daily [QD] and 3.0 mg QD) in male and female subjects aged 50 to 85 years who have dementia-related apathy.

Approximately 150 subjects are planned to be screened to achieve approximately 75 subjects randomly assigned to CVL-871 1.0 mg QD, CVL-871 3.0 mg QD, or placebo QD in a 1:1:1 fashion (25 per treatment group). Randomization will be stratified by 2 distinct strata: 1) subjects currently using selective serotonin reuptake inhibitor (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) during the trial, 2) subjects not using SSRIs or SNRIs at the time of randomization.

The trial protocol was amended (Protocol Version 4) to allow the trial to be considered as complete with 60 randomized subjects in the event of significantly slower recruitment rate than anticipated to avoid unduly long delay of the final analysis. However, as indicated in Section 1, the sponsor in November 2024 made further decision to discontinue enrollment due to slow recruitment.

3.2. Study Overview

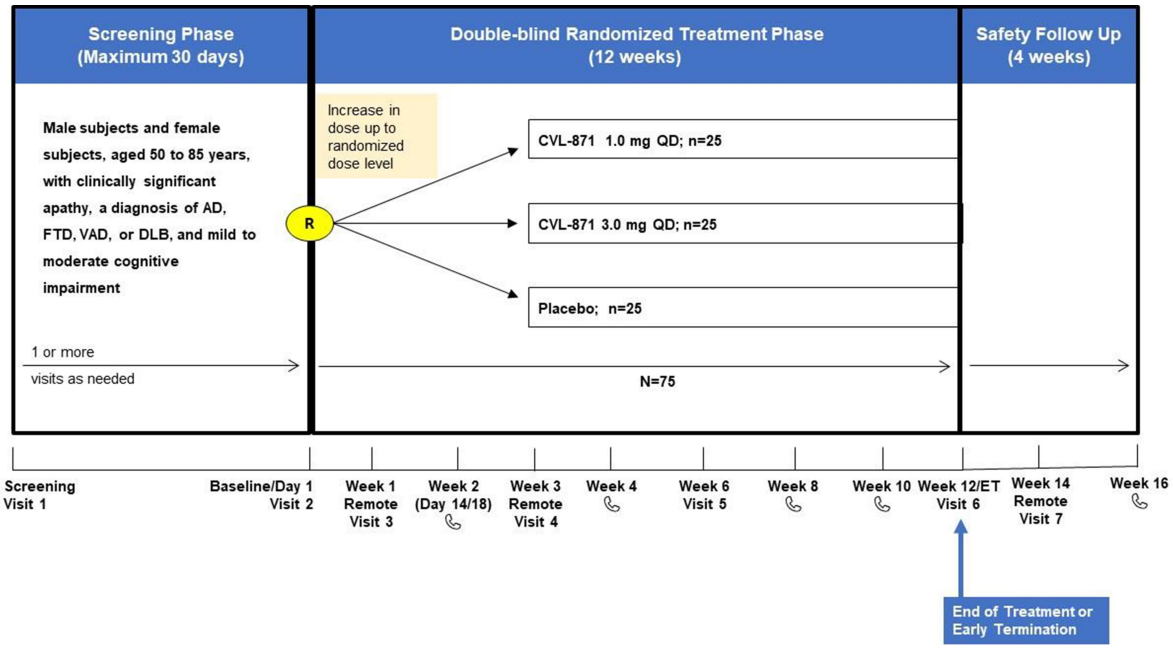
The study will comprise of:

- Screening Period: Up to 30 days from signed informed consent (up to Day -31 to -1 from Baseline): Participants will be evaluated according to inclusion and exclusion criteria
- Baseline (Day 1): Participants who remain eligible will be randomized
- 12-week double-blind placebo-controlled treatment period: Participants will be randomized to receive either CVL-871 1.0 mg, CVL-871 3.0 mg, or placebo
- 4-week post treatment follow-up safety period

The end of the study (EOS) is defined as the date of the last visit (including phone contact) of the last subject in the trial globally.

The trial design is depicted in Figure 1.

Figure 1: Trial Schematic



Abbreviations: AD=Alzheimer's disease; DLB=dementia with Lewy bodies; ET=Early Termination; FTD=frontotemporal dementia; QD=once daily; VAD=vascular dementia.

3.3. Treatments

CVL-871 is a D1/D5 receptor partial agonist and can provide increased dopaminergic stimulation without the abuse liability and potential for cardiovascular and other systemic side effects associated with psychostimulants. Based on previous exposure data, the top dose of 3 mg QD is the maximum dose that can be administered without exceeding the exposure limiting criteria based on nonclinical toxicological data.

Evaluation of 2 fixed doses with distinctly different levels of target occupancy in this exploratory trial will facilitate the determination of a dose range for D1 partial agonist therapy for dementia-related apathy in subsequent trials as well as support evaluation of the dose relatedness of the response. The study will, therefore, evaluate CVL-871 1.0 mg QD, CVL-871 3.0 mg QD versus placebo QD. The investigational medicinal products (IMPs) will be taken orally.

3.4. Dose Adjustment/Modifications

In order to mitigate the effects of nausea and vomiting, the target doses of CVL-871 will be titrated to the target dose using a fixed titration scheme as shown in Table 2.

Table 2: Treatment Dosing Schedule

Trial Day (Expected Number of Days)	Titration Step	Target Dose		Placebo QD
		CVL-871 1.0 mg QD	CVL-871 3.0 mg QD	
Days 1-3 (3)	Step 1	0.25 mg CVL-871 QD	0.25 mg CVL-871 QD	Placebo QD
Days 4-7 (4)	Step 2	0.5 mg CVL-871 QD	0.5 mg CVL-871 QD	Placebo QD
Days 8-16 (9)	Step 3	1.0 mg CVL-871 QD	1.0 mg CVL-871 QD	Placebo QD
Days 17-21 (5)	Step 4	1.0 mg CVL-871 QD	2.0 mg CVL-871 QD	Placebo QD
Days 22-84 (63)	Step 5	1.0 mg CVL-871 QD	3.0 mg CVL-871 QD	Placebo QD

Abbreviation: QD=once daily.

The starting dose for titration, 0.25 mg/day, is anticipated to be well tolerated with minimal nausea. Also, dose increments every 3 to 4 days were proven successful in achieving the target dose of 3 mg in healthy subjects in past studies, with minimal tolerability issues. Moreover, for subjects who do experience tolerability issues associated with dose increases at prespecified timepoints during the trial, down titration options will be available to improve tolerability.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. Sample Size Considerations

While formal hypothesis testing is not the key objective of this trial, the original planned sample size of approximately 75 subjects randomized in a 1:1:1 manner between the placebo and 2 CVL-871 arms should allow the trial to have approximately 80% probability to detect an effect size (treatment difference/population standard deviation [SD]) of 0.678 in change from Baseline on the Neuropsychiatric Inventory (NPI) apathy domain score at Week 12 between an active dose group and placebo, at a 2-sided alpha = 0.2 level (ie, an 80% confidence interval [CI] excluding zero). As a reference, in the ADMET 1 trial (6 weeks of treatment with methylphenidate for apathy in Alzheimer's disease), an effect size 0.5625 (mean difference of 1.8 and SD of 3.2) on the change from baseline in the NPI apathy domain score was observed (Rosenberg et al, 2013). A discontinuation rate of 20% was taken into consideration in the sample size calculation.

At the time of protocol amendment Version 4.0, an assessment of the detectable treatment effect with a sample size of 60 subjects (randomized 1:1:1 to the 3 treatment groups) concluded that an effect size of 0.761 can be detected with 80% power at a 2-sided alpha level of 0.2.

4.2. Randomization, Stratification, and Blinding

During the entire trial, treatment will be double-blind. Treatment assignments will be based on a computer-generated randomization code provided by Cerevel or designee. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the Interactive Response Technology (IRT), and reporting Serious Adverse Events (SAEs) to regulatory agencies. Once a randomization number has been assigned, it must not be reassigned. A participant cannot be randomized more than once in the study.

Randomization will be stratified according to 2 distinct strata:

- Subjects currently using SSRIs or SNRIs during the trial
- Subjects not using SSRIs or SNRIs

The CVL-871 and placebo tablets will be identical in appearance and will be packaged in identically appearing bottles. All subjects will take a single tablet, either CVL-871 or placebo, once daily throughout the Treatment Period. Tablets will be packaged to allow dosage adjustments to be made without breaking the trial blind.

Documentation of breaking the blind should be recorded on the subject's medical record with reason for breaking the blind, the date and time the blind was broken, and the names of the personnel involved. Once the blind is broken for a subject, reinitiation of treatment with IMP cannot occur for that subject.

4.3. Analysis Sets

Participants exposed to IMP before or without being randomized will not be considered randomized, will not be included in any analysis set and will be reported in listings under a study

intervention group named “not randomized but treated”. However, if these participants experienced any safety event, they would be documented separately in the Clinical Study Report (CSR). Participants who are randomized but not treated will not be included in pharmacodynamics (PD), safety, nor pharmacokinetics (PK) analyses. They will only be included in the description of demographic and baseline characteristics. In the tables, they will be part of the treatment group they have been randomized into. In the listings, they will be presented in a “Randomized, not treated” by-line statement, which will be presented prior any other treatment group.

Population	Description	Analysis	Treatment Group
Screened	All subjects who consent to participate in the clinical trial.	NA	NA
Intent-to-Treat (ITT)	All randomized subjects.	Demographic and Baseline Characteristics	Planned
Modified ITT (mITT)	A subset of ITT with randomized subjects who tolerate dose increases to at least Step 4 on Day 21 during titration and have at least 1 post-baseline assessment of the NPI-C apathy subscale score.	Primary analysis set for PD	Planned
Full Analysis Set (FAS)	All randomized subjects who received at least 1 dose of IMP.	Safety analysis	Actual
Pharmacokinetic analysis set (PK set)	All randomized subjects who receive at least 1 dose of IMP and have at least one measurable CVL-871 concentration.	PK analysis	Actual

Abbreviations: IMP=investigational medicinal product; NA=not applicable; NPI-C=Neuropsychiatric Inventory-Clinician; PD=pharmacodynamics; PK=pharmacokinetic.

4.4. Reporting Conventions

Statistical analysis will be performed using SAS® Version 9.4 or higher.

Standardized and validated SAS macros from PPD will be used to set-up table, listing, figure (TLF) formats (headers/footers and tabulation format) and to tabulate the summaries. All tables and listings will be independently validated using double programming; all figures will be independently validated manually.

4.4.1. Treatment Labels

Table 3: Treatment Order and Labels

Treatment Order	Treatment Group	Treatment Label
1	CVL-871 1.0 mg QD	CVL-871 1.0 mg QD
2	CVL-871 3.0 mg QD	CVL-871 3.0 mg QD
3	Placebo	Placebo
4	CVL-871 Combined	CVL-871 Combined
5	Total	Total

Abbreviations: QD=once daily.

4.4.2. Visit Naming Conventions

The eCRF visit label will be used to classify the assessments.

4.4.3. Visit Windows

Analysis data will be summarized according to the scheduled visit time period for which they were recorded in the eCRF unless otherwise specified.

4.4.4. Unscheduled Visits

Unscheduled assessments will not be slotted to a particular time point, but will be used when determining the worst-case value. All unscheduled visits will be included in listings.

4.4.5. Display of Data Summary and Analysis

Continuous variables will be summarized using descriptive statistics, including the following: sample size (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum for each treatment group.

All mean, Q1, Q3 and median values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value.

Confidence intervals (CIs) will be two-sided and displayed to the same level of precision as the statistics they relate to. If an estimate or a CI is not estimable, it will be presented as ‘NE’. If neither an estimate, nor its CI are estimable, it will be presented as simply ‘NE’, not displaying ‘NE’ twice.

The p-values will be two-sided and 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’.

Categorical and ordinal data will be summarized using the counts and percentages. When count data are presented, the percent 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

for demographics, baseline characteristics and compliance to account for missing values. No percentages will be displayed on the 'Missing' rows and the percentages on the other rows will be based on the number of non-missing observations. Unless otherwise specified, the denominator for all other percentages will be the number of participants in that treatment within the specific analysis set of interest. All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses. When the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0).

All listings will be sorted for presentation in order of assigned treatment arm, study center number, participant number and date of procedure or event.

4.4.6. Baseline, Study Day and Duration Derivations

The baseline value of efficacy parameters is defined as the last available valid (non-missing) value up to randomization.

The baseline value of safety parameters is defined as the last available valid (non-missing) value prior to the first dose of IMP. For participants randomized and not treated, the baseline value is defined as the last available valid (non-missing) value obtained up to the date and time of randomization.

Baseline safety and pharmacodynamic results are presented in the safety and pharmacodynamic analyses.

The safety and PK analyses reference day (denoted as Day 1) for the calculation of study day of safety and PK assessments will be the date of first dose of IMP. The reference day (denoted as Day 1) for the calculation of study day of pharmacodynamic assessments will be the randomization date.

- For visit prior to the reference day, study day = assessment date – reference date.
- For visit at or after the reference day, study day = assessment date – reference date + 1.

Intervals that are presented in weeks will be transformed from days to weeks by using (without rounding) the following conversion formula:

WEEKS = DAYS /7

Intervals that are presented in months will be transformed from days to months by using (without rounding) the following conversion formula:

MONTHS = DAYS /30.4375

4.4.7. Change From Baseline and Percent Change From Baseline

Change from baseline is defined as: Change from baseline = Value at specific time point – Baseline value

Percent change from baseline is defined as:

$$\text{Percent change from baseline}(\%) = \frac{\text{Value at specific timepoint} - \text{Baseline value}}{\text{Baseline value}} \times 100\%$$

5. SUBJECT DISPOSITION

5.1. Disposition

The patient disposition will be summarized for the screened set by treatment group and overall using number and percentage. This section describes patient disposition for both patient study status and the patient analysis sets.

For patient study status, the number and percentage of patients in the following categories will be presented:

- Screened patients
- Screen failure patients
- Patients treated without being randomized
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who permanently discontinued treatment (by reason)
- Patients who have completed the study treatment period as scheduled
- Patients with premature end of study (by reason)
- Patients who completed study

For screened, screen failure, and patients treated without being randomized, percentages will be calculated using the number of screened patients as the denominator for overall only. All other categories of patients will be presented by treatment group and for overall whilst the percentages will be calculated using the number of randomized patients within each treatment group and overall, as denominator. Reasons for treatment discontinuation will be supplied in tables showing number and percentage by treatment group. A CONSORT diagram summarizing the patient disposition will also be constructed.

Listings of randomization assignment and drug actually received will be provided by participant. If applicable, patients randomized but not treated and those whose randomization code was broken will be identified and described in separate listings. Additionally, a summary of the analysis sets for screened, intent-to-treat (ITT), modified intent-to-treat (mITT), full analysis set (FAS), and PK will be provided by treatment group and overall using number and percentage.

A listing of patients excluded from analysis sets will be provided. Patients with permanent treatment discontinuation (early withdrawals) will be identified and described in separate listings.

The disposition of screened patients by country and site will be summarized for the screened analysis set by treatment group and overall using number and percentage.

5.2. Protocol Deviations

All important protocol deviations including randomization and drug-dispensing irregularities will be summarized in general and according to COVID-19 impact (ie, deviations related to COVID-19 pandemic and deviations not related to COVID-19 pandemic) for the ITT analysis set by treatment group and overall using number and percentage.

A listing of all protocol deviations will be provided. A summary table of patients with at least one important protocol deviations will be provided.

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the critical or major irregularities will be categorized and summarized for the ITT analysis set by treatment group and overall using number and percentage.

A listing of patients with at least one important protocol deviation related to randomization and drug-dispensing irregularities will be provided.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
• Kit dispensation without IRT transaction • Erroneous kit dispensation • Kit not available • Randomization by error • Patient randomized twice • Forced randomization • Stratification error • Patient switched to another site

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics, patient characteristics and baseline disease characteristics will be summarized using the ITT analysis set by treatment group and overall using descriptive statistics or using number and percentage. P-values on the treatment difference for the demographic and baseline characteristics data will not be calculated. In general, no specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety/pharmacodynamic analysis.

6.1. Demographics

The following demographics and patient characteristics will be summarized by treatment group and overall:

- Age (years),
- Age categories (<75, ≥75),
- Gender (Male, Female),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple),
- Baseline body weight (kg) with grouping (<70, ≥70 to <100, ≥100),
- Baseline height (cm),
- Baseline body mass index (BMI) (kg/m^2) derived as: (Weight in kg)/(Height in meters)^2,
- Baseline BMI categories (<25, ≥25 to <30, ≥30).

The categories presented above may be modified in case of too few subjects (≤3).

Patient demographic and baseline characteristics will also be presented in a listing.

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall:

- Diagnostic criteria for apathy (DCA) by criterion: A, B, C, D (yes, no)
- Primary diagnosis (AD, FTD, VAD, or DLB), based on Dementia History
- Mini-Mental State Examination (MMSE) (<12, ≥12 to ≤26, >26)
- Dementia History (see Section 6.5)
- Baseline NPI Apathy/Indifference score
- Baseline NPI-C Apathy score
- Baseline DAIR score

- Baseline AES-C score
- Baseline ADAS-Cog score
- Randomization stratum of concomitant use of SSRI/SNRI (Yes, No)
- Catechol-o-methyltransferase (COMT) status (Val/Val, Met/Val, Met/Met)

Clinical Dementia Rating (CDR) was removed as an inclusion/exclusion criterion from protocol (Amendment Version 3.0), and scores for patients with CDR scores will be listed, as well as other baseline disease characteristics.

6.3. Alcohol and Drugs Usage

Substance use, amount and frequency will be collected in the CRF at baseline and usage (current, previous, never) will be summarized by treatment group and overall. A listing will be displayed with all information collected in the CRF at baseline.

6.4. Medical History

6.4.1. General Medical History

Medical and psychiatric history includes all the relevant medical and psychiatric history during the lifetime of the patient.

Medical and psychiatric history will be coded to “preferred term (PT)” and associated primary “system organ class (SOC)” using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of database lock.

The number and percentage of participants with any medical and psychiatric history will be summarized by treatment group and overall and by each SOC and PT. SOC will be sorted in descending order of frequency based on the total of all treatment groups. A listing will be provided.

6.4.2. Dementia History

Dementia history (type and time since diagnosis) will be summarized as part of the baseline disease characteristics.

6.5. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be presented for the screened analysis set for each treatment group and screen failure subjects using number and percentage. A listing of excluded patients with the met/unmet inclusion/exclusion criteria will be provided.

7. TREATMENTS AND MEDICATIONS

7.1. Prior, Concomitant and Post-Treatment Medications

The prior and concomitant medications will be presented for the ITT analysis set for each treatment group and overall using number and percentage. No statistical test for the between-group difference will be performed.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version in effect at the time of database lock.

Medications will be summarized by treatment group according to the WHO-DD, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, patients may be counted several times for the same medication.

The summaries for prior, concomitant and post-treatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the total incidence across treatment groups. In case of equal frequency regarding ATCs, alphabetical order will be used.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as described in Section 17.2.2. Prior, concomitant, and post-treatment medications, their start/end dates and frequencies will be presented in a listing.

7.1.1. Prior Medications

Prior medications are those the patient began prior to first IMP intake. Prior medications can be discontinued before first treatment administration or can be ongoing during the treatment phase.

7.1.2. Concomitant Medications

Concomitant medications are any treatments received by the patient concomitantly to the IMP, starting from the 1st administration of IMP to the date of last administration. A given medication can be classified both as a prior medication and as a concomitant medication.

7.1.3. Post-Treatment Medications

Post-treatment medications are those the patient took (continued or initiated) in the period running from the day after the last administration of IMP up to the end of the study.

7.2. Study Treatments

7.2.1. Extent of Exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as (last IMP administration dose date – first IMP administration dose date + 1 day), regardless of unplanned intermittent discontinuations. Last IMP administration date is defined as the last available administration date in the "Exposure" form. The reason for early treatment discontinuation will also be based on this last available Exposure form.

Duration of IMP exposure (in weeks) will be summarized descriptively as a quantitative variable (number, mean, SD, median, Q1, Q3, minimum and maximum). In addition, duration of IMP exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- >0 and ≤3 weeks
- >3 and ≤6 weeks
- >6 and ≤12 weeks
- >12 weeks

The extent of IMP exposure will be assessed and summarized by actual treatment group and overall for the FAS.

7.2.2. Treatment Compliance and Modifications

Percentage of compliance will here only be calculated and considered from the day after last up-titration, ie, per schedule, from Day 23 on. In this setting, percentage of compliance for a patient will be defined as the number of tablets the patient has taken (# of dispensed - # of returned -1) divided by the total number of tablets that the patient was planned to take during the last treatment period (from Day 23 [the day after Visit 4]on to the last date of IMP administration). That is, for patients taking IMP till at least Day 23, we define the following:

$$\text{Percentage of compliance (\%)} = \left[\left(\#\ of\ dispensed\ -\ \#\ of\ returned\ -1 \right) \Big/ \text{(Final) Dosing Stop Date-(Final) Dosing Start Date+1} \right] \times 100\%$$

Percentage of compliance will be summarized descriptively as a quantitative variable (number, mean, SD, median, Q1, Q3, minimum and maximum). In addition, the percentage of compliance will be presented by the specific ranges for each treatment group:

- <80%
- ≥80% to <120%
- ≥120%

Dose modification of IMP for an individual patient is not allowed and therefore no summary of dose modifications will be provided. Down titrations allowed per protocol will be summarized.

8. EFFICACY ANALYSIS

Not applicable.

9. SAFETY ANALYSIS

All randomized subjects who received at least one dose of IMP will be included in the safety analysis. All results will be summarized using the FAS by actual treatment group and CVL-871 Combined, which is defined as combined CVL-871 treatment groups.

The observation periods include:

- The pre-treatment period is defined as the time up to first administration of the IMP.
- The on-treatment period is defined as the time from the first administration of the IMP (on Day 1) to the last administration of the IMP + 28 days.
- The post-treatment period is defined as the time from the last administration of the IMP + 29 days to the end of the study follow-up.

9.1. Adverse Events

The adverse event (AE) types include:

- **Pre-treatment adverse events** are adverse events that developed up to the first administration of the IMP.
- **Treatment-emergent adverse events** (TEAEs) are adverse events that developed or worsened or became serious during the treatment period.
- **Post-treatment adverse events** are adverse events that developed or worsened or became serious after the treatment period.

The primary focus of adverse event reporting will be on TEAEs. Pre-treatment and post-treatment adverse events will be summarized separately.

All AEs will be coded to a PT and associated primary SOC using the version of MedDRA in effect at the time of database lock.

Adverse events will be recorded from the time of signed informed consent until the end of the study or the resolution/stabilization of all SAE and adverse event of special interest (AESI).

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment-emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 17.2 .

Adverse events will be summarized by primary SOC and PT, sorted by the internationally agreed SOC order (MedDRA® Data Retrieval and Presentation: Points to Consider, 2022) and decreasing frequency of PTs in high dose group within SOC unless otherwise specified. In case of equal frequency regarding PTs, alphabetical order will be used. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages will be the FAS within each treatment group.

On top of the analysis planned below, all TEAEs, all treatment emergent SAEs, TEAEs leading to permanent treatment discontinuation and TEAEs leading to death will be summarized by treatment group.

Overview summaries of the number and percentages of patients within the following categories will be provided by treatment group and overall for:

- Any TEAE
- Any study drug related TEAE
- Any TEAE of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher
- Any Serious TEAE
- Any Serious TEAE considered study drug related
- Any TEAE leading to permanent treatment discontinuation
- Any TEAE of special interest
- Any Serious TEAE of special interest
- Any AE leading to death

The overview summaries for pre-treatment AEs, TEAEs and post-treatment AEs will be provided based on the FAS.

Individual listings (AEs, SAEs, AEs leading to permanent treatment discontinuation, AEs leading to death, AESI) will be provided to support the summary tables based on the FAS.

9.1.1. Incidence of Adverse Events

The following TEAE summaries will be generated for the FAS, for each treatment group and overall.

- All TEAEs presented by PT, showing number and percentage of patients with at least 1 TEAE, sorted by decreasing incidence of PT in the high dose treatment group
- All pre-treatment AE presented by primary SOC and PT, showing number and percentage of patients with at least 1 AE
- All TEAEs presented by primary SOC and PT, showing number and percentage of patients with at least 1 TEAE
- All post-treatment AE presented by primary SOC and PT, showing number and percentage of patients with at least 1 AE
- Common TEAEs (PTs with an incidence ≥5% in any treatment group) by primary SOC and PT
- Common TEAEs (PTs with an incidence ≥2% in either CVL-871 treatment group and greater than placebo group) by primary PT

- Relationship of adverse events to study drug

The following TEAE summaries will be generated for the FAS, for each treatment group and overall:

- All TEAEs by relationship, presented by primary SOC and PT, showing the number and percentage of patients with at least 1 TEAE

9.1.2. CTC Grade of Adverse Events

The following TEAE summaries will be generated for the FAS, for each treatment group and overall.

- All TEAEs by maximal reported CTCAE grade, presented by primary SOC and PT, showing the number and percentage of patients with at least 1 TEAE by maximal CTCAE grade.

9.1.3. Serious Adverse Events

The following TEAE summaries will be generated for the FAS, for each treatment group and overall.

- All serious TEAEs, presented by primary SOC and PT, showing the number and percentage of patients with at least 1 serious TEAE
- All serious TEAEs by relationship, presented by primary SOC and PT, showing the number and percentage of patients with at least 1 serious TEAE

9.1.4. Adverse Events Leading to Permanent Treatment Discontinuation

The following TEAE summaries will be generated for the FAS, for each treatment group and overall.

- All TEAEs leading to permanent treatment discontinuation, presented by primary SOC and PT, showing the number and percentage of patients with at least 1 TEAE leading to permanent treatment discontinuation

9.1.5. Adverse Events Leading to Study Discontinuation

The following TEAE summaries will be generated for the FAS, for each treatment group and overall.

- All TEAEs leading to study discontinuation, presented by primary SOC, and PT, showing the number and percentage of patients with at least 1 TEAE leading to study discontinuation

9.1.6. Adverse Events of Special Interest (AESI) as Defined in Protocol

As defined in CSP Section 8.4.6, Adverse Events of Special Interest (AESI) include:

- Symptoms suggestive of symptomatic orthostatic hypotension:
  - Syncope

  - Presyncope requiring stabilization to avoid fall
  - Generalized weakness, sensations described as dizziness or lightheadedness, visual blurring or darkening of the visual fields, and, in severe cases, loss of consciousness
- Grade 3 nausea, defined as inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition, or hospitalization indicated
- Grade 2 vomiting, defined as vomiting requiring outpatient intravenous hydration or other medical intervention (eg, anti-emetic)
- Abnormal liver function tests:
  - Treatment-emergent value of >3 × the upper limit of normal (ULN) for ALT or AST and >2 × ULN for total bilirubin
  - Treatment-emergent value of >3 × ULN for ALT or AST and clinical jaundice
- Abnormal dreams/nightmares
- Adverse events potentially related to abuse (as provided in the Abuse Potential Monitoring Plan [APMP])
- Adverse events leading to discontinuation of IMP or from the trial

The following AESI summaries will be generated for the FAS, for each treatment group and overall.

- All TEAEs of special interest, presented by primary SOC and PT, showing the number and percentage of patients with at least 1 TEAE of special interest
- All serious TEAEs of special interest, presented by primary SOC and PT, showing the number and percentage of patients with at least 1 serious TEAE of special interest

9.1.7. Adverse Events Leading to Death

The following TEAE summaries will be generated for the FAS, for each treatment group and overall.

- All TEAEs leading to death (death as an outcome on the eCRF form "Adverse Event" as reported by Investigator), presented by primary SOC and PT, showing the number and percentage of patients with at least 1 TEAE leading to death

9.1.8. Death

The following summaries of deaths will be generated for the FAS, for each treatment group and overall:

- Number and percentage of patients who died during the trial by study period (ie, TEAE period, post-treatment period) and by cause of death
- Number and percentage of non-randomized patients or randomized but not treated patients who died

A listing of all patients who died at any time during the study will be provided.

9.2. Clinical Laboratory Evaluations

The laboratory tests will be performed by the local laboratories according to routine clinical practice at site and country level. The Investigator will review the laboratory report, document this review, and record any clinically relevant findings/changes occurring during the study in the AE section of the CRF.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations; any clinically significant abnormal lab values will be included in the adverse event analyses.

9.2.1. Hematology

Blood for safety laboratory samples will be collected at Screening, Baseline and Weeks 1, 3, 6, 12, and 14. The following parameters will be captured:

- Platelet count
- Red blood cell count
- Hemoglobin
- Hematocrit
- Mean corpuscular volume
- White blood cell count with differential:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils

Summary statistics for actual and change from baseline value will be provided by visit and treatment group. The number of subjects with on-treatment CTCAE Grade 3-5 will be summarized for each parameter.

Shift tables between baseline and on-treatment (based on worst-case on-treatment change from baseline) will also be presented for each parameter. Categories will be “low” (define as a value below the normal range), “normal” and “high” (define as a value above the normal range). Additionally, all relevant data will be listed for the FAS.

9.2.2. Clinical Chemistry

Clinical chemistry for safety laboratory will be collected at Screening, Baseline and Weeks 1, 3, 6, 12, and 14. Results are to be directly transferred to clinical database (not to be recorded on the eCRFs); any clinically significant abnormality will be captured as an AE.

Clinical chemistry collected parameters will include:

- Blood urea nitrogen
- Creatinine
- Albumin
- Cholesterol (total, HDL-C, LDL-C)
- Triglycerides
- Potassium
- Sodium
- Calcium
- Bicarbonate
- Chloride
- Magnesium
- Glucose
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Gammaglutamyl transferase (GGT)
- Creatine phosphokinase (CPK)
- Total bilirubin and direct bilirubin
- Total protein
- Serum prolactin

Summary statistics for actual and change from baseline value will be provided by visit and treatment group. The number of subjects with on-treatment CTCAE Grade 3-5 will be summarized for each parameter.

Shift tables between baseline and on-treatment (based on worst-case on-treatment change from baseline) will also be presented for each parameter. Categories will be “low” (define as a value below the normal range), “normal” and “high” (define as a value above the normal range). Additionally, all relevant data will be listed for the FAS.

9.2.3. Urinalysis

Urine for safety laboratory will be collected at Screening, Baseline and Weeks 1, 3, 6, and 12. Urinalysis results are not to be recorded on the eCRFs; any clinically significant abnormality will be captured as an AE.

Urinalysis collected parameters will include:

- Specific gravity
- Color
- pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
- Microscopic examination (if blood or protein is abnormal)

All urine laboratory data will be listed for the FAS.

9.3. Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressures, heart rate, and body temperature. Duplicate blood pressure and heart rate measurements will be obtained sitting/supine (after 5 minutes of rest) followed by a single standing measurement (after 2 minutes of rising from sitting/supine position). The duplicate values (sitting/supine) will be individually recorded, and the values will be averaged by the sponsor for the time point assessment. At each visit, body temperature will be obtained once, at the time of the first blood pressure measurement. Orthostatic blood pressure parameters are calculated as the average measurement in the sitting/supine position minus the measurement in the standing position for the corresponding parameters, for each visit.

Potential clinically significant values and changes of vital signs parameters are:

- Weight: weight gain or loss >7% from baseline
- Systolic blood pressure (sitting/supine average)
  - Max observed value >160 mmHg
  - Max increase from baseline >20 mmHg
  - Min observed value <90 mmHg
  - Greatest decrease from baseline >20 mmHg
- Orthostatic Systolic Blood Pressure
  - Greatest decrease upon standing compared with sitting/supine position ≥20 mmHg
  - Max increase upon standing compared with sitting/supine position ≥20 mmHg
- Diastolic blood pressure (sitting/supine average)
  - Max observed value >100 mmHg
  - Max increase from baseline >10 mmHg
  - Min observed value <50 mmHg
  - Greatest decrease from baseline <10 mmHg
- Orthostatic Diastolic Blood Pressure

  - Greatest decrease upon standing compared with sitting/supine position ≥10 mmHg
  - Max increase upon standing compared with sitting/supine position ≥10 mmHg
- Heart Rate (sitting/supine average)
  - Max observed value >120 bpm
  - Min observed value <50 bpm

Vital signs data including changes from baseline will be summarized through descriptive statistics by visit and treatment group. Potential clinically significant values and changes defined above will be summarized based on the maximum/minimum actual post-baseline values and maximum increase/greatest decrease from baseline. Additionally, all relevant data will be listed for the FAS.

9.4. Physical and Neurological Examination

A full physical examination will consist of measurement of height (screening only) and weight and a review of the following body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, and musculoskeletal systems.

A full neurological examination will include an assessment of the subject's mental status (level of consciousness, orientation, speech, memory, etc), cranial nerves, motor (muscle appearance, tone, strength and reflexes), sensation (including Romberg sign), coordination, and gait.

Results (normal, abnormal, or not done) from the assessment will be reported. All deviations from normal will be recorded, including those attributable to the patient's disease.

Any condition present at the on-treatment and post-treatment physical and neurological examinations that was not present at the baseline examination will be documented as an AE.

Physical and neurological examination will be presented as a listing of abnormal physical and neurological examination. Medical history will be presented in a separate listing.

9.5. Electrocardiogram

At Screening, a triplicate set of 12-lead electrocardiograms (ECGs) will be obtained to assess subject eligibility. Based on the QT interval as corrected for heart rate by Fridericia's formula (QTcF), a subject will be excluded if the average QTcF interval of the triplicate set of screening ECGs is ≥450 msec, as read by the central ECG service.

At all other time points (Baseline, Weeks 1, 3, 6, 12, and 14) a single ECG will be performed and evaluated at the investigational site to monitor safety during the trial. Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be used for reading all ECGs in order to standardize interpretations for the safety analysis.

ECG data including changes from baseline will be summarized through descriptive statistics by visit and treatment group. A shift table of the number and percentage of subjects who had normal and abnormal ECG findings will also be displayed by visit and treatment group.

The number and percentage of patients with notable QTcF interval prolongation, ie,

- >450 and ≤480 msec,
- >480 and ≤500 msec,
- >500 msec

and change from baseline into the intervals

- >30 and ≤60 msec increase,
- >60 msec increase

will be displayed by treatment group, using the worst post-baseline value. Listings of ECG findings and a listing of ECG values will be provided.

9.6. Other Safety Data

C-SSRS Columbia-Suicide Severity Rating Scale (C-SSRS) will be collected at Screening, Baseline and Weeks 1, 3, 6, 12 and 14 and used to monitor suicidality.

This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version will be completed for all subjects at screening to determine eligibility whereas the "Since Last Visit" C-SSRS form will be completed at all visits after screening.

The C-SSRS is comprised of 10 categories with binary responses. The 10 categories include:

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

Categories 1-5 represent Suicidal Ideation and categories 6-10 represent Suicidal Behavior. Each category is scored as 1 if there is a positive response in the category and a 0 otherwise. The Suicidal Ideation Score is the maximum suicidal ideation category that has a positive response and is 0 otherwise, that is, the Suicidal Ideation Score ranges from 0 to 5.

The maximum post-baseline result from the C-SSRS will be summarized for the FAS. The maximum of each subscale (suicidal ideation [Categories 1-5], suicidal behavior [Categories 6-10], suicidal ideation or behavior [Categories 1-10], and self-injurious behavior without suicidal intent) will be presented by treatment group. Note that the maximum is either 0 or 1. The number and percentage of patients with increased and decreased max post-baseline values of Suicidal Ideation Score compared to baseline values will be presented by treatment group. All C-SSRS elements will be reflected in a listing.

10. PHARMACOKINETICS

Single blood samples will be collected in appropriately labeled tubes for determination of the concentration of CVL-871 in plasma at Weeks 1, 3, 6, and 12.

Plasma concentration data of CVL-871 will be summarized for each dose at each time point using descriptive statistics and graphs based on all randomized subjects who received at least one dose of IMP and had at least one measurable CVL-871 concentration result. Additionally, all data will be listed for PK set. The descriptive statistics for PK concentrations will include geometric mean and geometric coefficient of variation (GCV) in addition to the descriptive statistics described in Section 4.4.5.

The geometric mean and GCV will be calculated based on the mean and variance of the logarithmic transformed data with the following formula to transform back:

Geometric mean = exp(mean), and

CV= 100*sqrt (exp(variance)-1).

11. PHARMACODYNAMICS

The planned timepoints for pharmacodynamic assessments are shown in the Schedule of Assessments (Table 4) which will be completed before the safety assessments and by the same identified caregiver.

All pharmacodynamic endpoints will be analyzed through descriptive statistical methods based on the mITT population. Pharmacodynamic endpoints with repeated post-baseline assessments will also be analyzed, using the mITT population, through statistical inference by using a mixed-model repeated measures (MMRM) analysis, including baseline score (if applicable), treatment, concomitant SSRI/SNRI use, visit (only measured at Visit 5 and 6), and the interaction between treatment group and visit as fixed factors in the model. Subject will be included as a random effect in the model.

An unstructured correlation matrix will be used to model the within-patient errors covariances. The Kenward-Roger approximation will be used to estimate the denominator of degrees of freedom. The least square (LS) mean of each treatment group, difference in the LS mean between the treatment groups, and the corresponding 80% and 95% CI of the differences and p-values will be provided.

If the MMRM model fails to achieve convergence due to complexity of model specification, different covariance structures will be used according to the following order till convergence is achieved:

1. Unstructured correlation (UN)
2. Heterogeneous Toeplitz (TOEPH)
3. Homogeneous Toeplitz (TOEP)
4. First-Order Autoregressive [AR(1)]
5. Compound Symmetry (CS)

The key research questions for the pharmacodynamic endpoints (ie, effect of CVL-871 treatment groups versus placebo) will be primarily addressed with a hypothetical strategy. As such, the missing values will be considered as missing at random (an MMRM analysis assumption).

The primary analysis for all PD endpoints will be performed as described above. However, if the number of subjects with evaluable baseline and post-baseline assessments for a specific PD endpoint is smaller than 15 (all treatment groups combined) or smaller than 2 in any treatment group, only descriptive statistical analyses will be conducted.

11.1. Neuropsychiatric Inventory-Clinician (NPI-C) and Neuropsychiatric Inventory Rating Scales

The NPI assesses 12 behavioral and psychiatric symptoms in dementia including domains for delusions, hallucinations, agitation/aggression, apathy, depression, euphoria, aberrant motor behavior, irritability, disinhibition, anxiety, sleeping, and eating (Cummings et al, 1994).

The NPI domain score for each domain is the product of frequency score × severity score reported by the caregiver in response to clinician administered questions specific to each domain. Higher scores are indicative of more frequent and/or severe symptoms.

The NPI-C is a revised version of the original NPI and includes expanded domains and domain subitems, and a clinician rated severity score as the principle scoring methodology (de Medeiros et al, 2010). Unlike the NPI, the NPI-C allows the rater to obtain additional caregiver and patient information to inform the rating for each item within a domain.

The frequency and the severity of each behavior item are determined on 5-point (0 to 4) and 4-point (0 to 3) scales, respectively, based on caregiver interview responses. An additional rating of caregiver distress is included (6-point scale from 0 to 5). The clinician also observes and interviews the patient, when possible, to inform on the frequency of symptoms and overall clinical presentation. The clinician provides a clinical impression severity score for each item within the domain using a 4-point (0 to 3) scale, which is based on all available clinical (eg, medical records, personal observations, personal experience and training) and interview information.

An NPI-C total domain score based on the clinician impression can be calculated by summing the individual rating score for each domain item. Higher scores are indicative of more frequent and/or severe symptoms.

The instrument can be used as a stand-alone measure for specific neuropsychiatric domains (eg, dysphoria, apathy) or a combination of both (combination of domains with focus on one or more specific domains). Only the NPI-C apathy and dysphoria domains will be utilized as assessment measures in this trial and changes from Baseline to Weeks 6 and 12 will be analyzed through an MMRM for the mITT as described in Section 11. Other NPI-C domains will not be utilized. The NPI will be utilized to assess all 12 neuropsychiatric domains, including apathy and dysphoria, for confirmation of inclusion/exclusion criteria and for ongoing evaluation during the treatment phase.

Each NPI domain will be analyzed separately using an MMRM when sample size allows. In addition, all NPI and NPI-C data will be listed for the randomized patients with indicator for inclusion in the mITT analysis set.

11.2. Dementia Apathy Interview and Rating (DAIR)

The DAIR is a 16-item structured interview with the primary caregiver designed to assess illness-related changes in motivation, emotional responsiveness, and engagement (Strauss and Sperry, 2002). Each interview question consists of 2 parts: 1) how often a specific behavior was observed over the past month, and 2) whether the behavior in first item had changed from the time prior to memory loss.

Apathy item scores range from 0 (patient shows apathetic behavior almost never or less than once a week) to 3 (patient shows apathetic behavior almost always or almost every day). In their original form, higher levels of apathy could correspond to higher or lower scores, depending on the questions. Therefore, questions will be rescaled as follows, so that higher rescaled scores correspond to higher levels of apathy. For questions 1, 9, 11, 12, 13, and 14, rescaled score = original score, and for questions 2 - 8, 10, 15, and 16, rescaled score = 3 - original score. Items are counted for the total score only if the behavior represents a change toward apathy from pre-illness behavior. The total apathy score is a sum of all items reflecting change, divided by the number of items completed, with higher scores representing greater average apathy.

Changes from Baseline to Visit 5 (Week 6) and Visit 6 (Week 12) in DAIR score will be analyzed through an MMRM for the mITT as described in Section 11. Individual DAIR items in their original form will be summarized through frequencies and percentages, regardless of whether or not they represented a change in apathy from pre-illness. Additionally, all DAIR individual related data will be listed for the randomized patients with indicator for inclusion in the mITT analysis set.

11.3. Apathy Evaluation Scale-Clinician (AES-C)

The AES-C is an 18-item rating scale which is completed by a clinician that measures apathy severity as defined by deficits in behavioral, cognitive, and emotional constructs of goal-directed behavior. Higher scores reflect greater apathy severity (Marin et al, 1991).

AES-C items are rated based on current subject's perception during the past 4 weeks. Ratings are based on the clinician's assessment of the patient's self-reports of AES-C items (perception during past 4 weeks) and rank from 1=Not at all characteristics to 4=A lot characteristic. In their original form, higher levels of apathy could correspond to higher or lower scores, depending on the questions. Therefore, questions will be rescaled as follows, so that higher rescaled scores correspond to higher levels of apathy. For questions 1-5, 7-9, and 12-18, rescaled score = 5 - original score, and for questions 6, 10, and 11, rescaled score = original score. AES-C total score is the total of items 1 through 18 after completion of the rescaling process and ranges from 18 to 72, with higher total scores corresponding to higher levels of apathy.

Changes from Baseline to Visit 5 (Week 6) and Visit 6 (Week 12) in AES-C score will be analyzed through an MMRM for the mITT as described in Section 11. Additionally, all AES-C related individual data will be listed for the randomized patients with indicator for inclusion in the mITT analysis set.

11.4. Alzheimer's Disease Assessment Scale – Cognition Subscale (ADAS-Cog)

The ADAS-Cog is the most widely used general cognitive measure in clinical trials of AD. The original ADAS-Cog (Rosen et al, 1984) includes 11 items assessing cognitive function. The domains include memory, language, praxis, and orientation.

The modified ADAS-Cog13 (Mohs et al, 1997), which will be used in this trial, includes all original ADAS-Cog items with the addition of a number cancellation task and a delayed free recall task, for a total of 85 points. As in the parent instrument, higher scores indicated greater severity. The questionnaire and the scores will be provided by WCG VeraSci.

Changes from Baseline to Week 12 in ADAS-Cog13 overall score will be summarized through descriptive statistics for the mITT set. Additionally, all individual related data will be listed.

11.5. Modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (mADCS-CGIC)

The original ADCS-CGIC focuses on clinicians' observations of change in the subject's cognitive, functional, and behavioral performance (Schneider et al, 2009). The original ADCS-CGIC has been modified specially for apathy in dementia.

Scoring is based on an interview with the caregiver by an independent, skilled, and experienced clinician with questions related to the severity of the subject's overall clinical condition and apathy symptoms specifically.

Scores are on a 7-point scale where 1 is "marked improvement" and 7 is "marked worsening" with a rating of 4 representing "no change". It is important to note that the assessment will reflect the subject's current condition compared with their condition at baseline (Visit 2).

A baseline worksheet will be completed by the rater to assist in making all post-baseline comparisons and ratings.

The questionnaire and the scores will be provided by WCG VeraSci.

Descriptive statistics of the mADCS-CGIC scores will be presented by visit. Additionally, all mADCS-CGIC related individual data will be listed.

11.6. Modified Clinical Global Impression-Severity Scale (mCGI-S)

The mCGI-S is an observer-rated scale that will be used to measure both the severity of the subject's overall clinical condition and their apathy symptoms specifically.

To perform this assessment, the investigator (or designee) will answer questions related to the severity of the subject's overall dementing illness (cognition, behavior, and function) and apathy symptoms specifically, providing a severity rating score based upon their total clinical experience with the patient population and upon observed and reported symptoms, behavior, and function in the past 4 weeks. Scores are on a 7-point scale where 1 is "normal, not at all ill/no symptoms" and 7 is "among the most extremely ill patients/very severe symptoms".

The questionnaire and the scores will be provided by WCG VeraSci.

Descriptive statistics of the mCGI-S scores will be presented by visit and change from Baseline to Visit 5 (Week 6) and Visit 6 (Week 12) in mCGI-S scores will be analyzed through an MMRM for the mITT as described in Section 11. Additionally, all mCGI-S related individual data will be listed for the randomized patients with indicator for inclusion in the mITT analysis set.

11.7. Caregiver Global Impression-Severity Scale (CaGI-S)

The CaGI-S is a caregiver-rated scale that will be used to measure both the severity of the subject's overall clinical condition and their apathy symptoms specifically.

To perform this assessment, the caregiver will answer the questions related to the severity of the subject's overall dementing illness (cognition, behavior, and function) and apathy symptoms specifically based upon their observations over the past 4 weeks.

Scores are on a 7-point scale where 1 is “normal, no symptoms of apathy/normal, not at all impaired” and 7 is “extremely severe apathy/extremely severely ill”.

The questionnaire and the scores will be provided by WCG VeraSci.

Descriptive statistics of the CaGI-S scores will be presented by visit and change from Baseline to Visit 5 (Week 6) and Visit 6 (Week 12) in CaGI-S scores will be analyzed through an MMRM for the mITT as described in Section 11. Additionally, all CaGI-S related individual data will be listed for the randomized patients with indicator for inclusion in the mITT analysis set.

11.8. Caregiver Global Impression-Change Scale (CaGI-C)

The CaGI-C is a caregiver-rated scale that will be used to measure change in both the subject’s overall dementing illness (cognition, behavior, and function) and their apathy symptoms specifically compared with before initiation of treatment with IMP. It is important to note that the caregiver will provide their assessment of the subject’s current condition compared with their condition at Baseline (Visit 2).

To perform this assessment, the caregiver will rate the subject’s change from baseline in their overall dementing illness (cognition, behavior, and function) and in their apathy symptoms specifically.

Scores are on a 7-point scale where 1 is “marked improvement in apathy/overall dementia” and 7 is “marked worsening in apathy/overall dementia”.

The questionnaire and the scores will be provided by WCG VeraSci.

Descriptive statistics of the CaGI-C scores will be presented by visit. Additionally, all CaGI-C related individual data will be listed.

12. INTERIM ANALYSIS

No interim analyses are planned in this study.

13. SUPPLEMENTARY ANALYSES

13.1. Adverse Events (Safety) By Treatment Period

The TEAE incidence will be summarized by two periods: Period 1 (Day 1 through Day 21; Step 1-4) and Period 2 (Day 22 through end of treatment) as well as TEAE incidence by actual dose level (0.25 mg, 0.5 mg, 1 mg, 2 mg, and 3 mg). The summary will be tabulated by SOC in internationally agreed order and PT in descending order of the higher dose group within SOC. Summary will also include a total column.

In addition, the incidence of TEAE leading to permanent discontinuation of treatment will be summarized by two periods: Period 1 (Day 1 through Day 21; Step 1-4) and Period 2 (Day 22 through end of treatment). The summary will be tabulated by SOC in internationally agreed order and PT in descending order of the higher dose group. Summary will also include a total column.

13.2. Impact of COMT (Val-Met) Status

Blood samples will be collected for analysis of catechol-O-methyltransferase (COMT) genotype. Sequencing was performed to detect the c.472G>A, p.Val158Met variant (Chr22:19951271) known familial variant ONLY. There will be one of three following results on the report,

- The variant of interest was NOT detected, corresponding to Val/Val
- The variant of interest was detected; heterozygous, corresponding to Met/Val
- The variant of interest was detected; homozygous, corresponding to Met/Met

The impact of COMT status on safety will be investigated by analysis of TEAEs, presented by primary SOC and PT, showing number and percentage of patients with at least 1 TEAE by COMT status (Met/Met vs Met/Val vs Val/Val) on the FAS.

To evaluate the impact of COMT status on pharmacodynamic, subgroup analyses will be conducted on the following pharmacodynamic endpoints based on the mITT set across the three COMT groups (Met/Met vs Met/Val vs Val/Val):

- NPI-C apathy domain score
- NPI apathy domain score
- DAIR score
- AES-C score

The subgroup analysis will be performed by subgroup rather than including an interaction term.

14. SUBGROUP ANALYSES

Subgroup analyses of the key pharmacodynamic endpoints, NPI-C apathy score and NPI apathy score will be made based on the mITT set to assess consistency of the intervention effect across the following subgroups:

- Age group (<75, ≥75)
- Sex: female vs. male
- Baseline NPI-C apathy score: ≤baseline median vs. >baseline median (median of the mITT set regardless treatment group)
- Use of concomitant SSRI/SNRI : yes vs. no

Provided that the sample sizes in the subgroups allow, the MMRM analysis method described in Section 11 will be applied to the subgroup analysis. The subgroup analysis will be performed by subgroup rather than including an interaction term. If the number of subjects within a subgroup is too small (less than 9 subgroup overall or less than 1 in any treatment group), only descriptive statistics will be used for the subgroup analysis.

15. CHANGES IN THE PLANNED ANALYSIS

In addition to changes corresponding to protocol amendments, the analysis plan differs from the protocol analysis section as shown below

- Protocol specified 80% CIs will be presented. The SAP further specifies that both 80% and 95% CIs will be included (Section 11).
- The population of all subjects who consent to participate in the clinical trial was referred as “Enrolled” in the protocol but is labeled as “Screened” for further clarity in the SAP (Section 4.3).
- The mITT population is modified in the SAP (Section 4.3) as compared with the protocol to allow analysis evaluates dose effect in this exploratory study.
- Due to the early closure of enrollment with the planned sample size not achieved, the hypothetical strategy is the only approach taken for missing value handling. The protocol specified sensitivity analyses are no longer planned.

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17. APPENDICES

17.1. Missing Efficacy Data

Not applicable.

17.2. Missing Safety Data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

17.2.1. Handling of Missing Age

If age is missing but year of birth is collected, then age will be derived as date of informed consent signed minus year of birth and June 30th, keeping the integer part of the result.

17.2.2. Handling of Medication Missing/Partial Dates

If a medication date or time is partially missing, it will be imputed in the most conservative way. That is, the start and end date will be set to the earliest and latest date, respectively, based on the partial date. If it cannot be determined whether it was taken prior, concomitantly, or post-treatment, it will be considered a prior, concomitant and post-treatment medication.

17.2.3. Handling of Adverse Events with Missing or Partial Date/Time of Onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment period, the adverse event will be classified as treatment emergent.

These data imputations are for categorization purposes only and will not be used in listings.

No imputation of adverse event end dates/times will be performed. No imputation is planned for date/time of adverse event resolution.

17.2.4. Handling of Adverse Events When Date and Time of First Investigational Medicinal Product Administration Is Missing

The first dose of IMP (at the Baseline Visit) will be taken in the clinic, which means missing date and time of first IMP administration is not expected.

17.2.5. Handling of Missing Assessment of Relationship of Adverse Events to Investigational Medicinal Product

If the assessment of the relationship to IMP is missing, then the relationship to IMP is assumed to be related and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

17.2.6. Handling of Missing Severity/Grades of Adverse Events

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered.

If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

17.3. Missing Pharmacodynamics Data

Since the MMRM used for inferential analyses of pharmacodynamics data is a type of statistical model that handles missing data, no imputation is foreseen.

17.4. Pharmacodynamic Test Scale Details

17.4.1. Neuropsychiatric Inventory-Clinician (NPI-C) and Neuropsychiatric Inventory Rating Scales

The Neuropsychiatric Inventory – Clinician Rating Scale (NPI-C)

Assessment Date:_____ Rater:_____ PT ID:_____

A. Delusions:

Does (S) have beliefs that you know are not true? For example, insisting that other people are trying to harm him/her or steal from him/her? Has he/she said that family members or staff are not who they say they are or that the house is not their home? I'm not asking about mere suspicions. I'm interested in whether (S) is convinced that these things are happening to him/her.
(✓) Yes: ☐No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) believe that he/she is in danger, that others are planning to hurt him/her or have been hurting him/her?					
2. Does (S) believe that others are stealing from him or her?					
3. Does (S) believe that his/her _____ is having an affair?					
4. Does (S) believe that unwelcome guests are living in his/her house?					
5. Does (S) believe that his/her family, staff members or others are not who they claim to be or that they are imposters?					
6. Does (S) believe that his/her house is not his/her home?					
7. Does (S) believe that family members plan to abandon him/her?					
8. Does (S) believe that television or magazine figures are actually present in the room? Does he/she try to talk or interact with them?					
*Do not leave blank. Enter "0" if it does not occur.				Column Total:	

B. Hallucinations:

Does (S) have hallucinations such as false visions or voices? Does (S) seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if (S) actually has abnormal experiences of sounds or visions? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) describe hearing voices or acts if he/she hears voices?					
2. Does (S) talk to people who are not there?					
3. Does (S) describe seeing things that are not present or acts like he/she sees things that are not present (people, animals, lights, etc.)?					
4. Does (S) report smelling odors not smelled by others?					
5. Does (S) describe feeling things on his/her skin or otherwise appear to be feeling things crawling on or touching him/her?					
6. Does (S) say or act like he/she tastes things that are not present?					
7. Does (S) describe any other unusual sensory experiences?					
*Do not leave blank. Enter "0" if it does not occur.				Column Total:	

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C. Agitation:

Is (S) hard to handle or uncooperative or resistive to care? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) get upset when people are trying to care for him/her or resist activities such as changing clothes?					
2. Is (S) stubborn, having to have things his/her way?					
3. Is (S) uncooperative or resistive to help from others?					
4. Does (S) ask repetitive questions or make repetitive statements?					
5. Does (S) seem restless in general?					
6. Is (S) unable to sit still or does he/she fidget constantly?					
7. Does (S) ask or complain about his or her health often, even though it is unjustified?					
8. Does (S) refuse to take medications?					
9. Does (S) pace nervously or angrily, in a way that differs from general wandering?					
10. Does (S) aggressively try to leave the residence or get to a different place (e.g., room)?					
11. Does (S) attempt to inappropriately use the phone in an attempt to get help from others?					
12. Does (S) hoard object?					
13. Does (S) hide objects					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

D. Aggression:

Does (S) shout angrily, slam doors, or attempt to hit or hurt others? Does (S) intentionally fall or try to harm him/herself?
(✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	Clinical Impression*
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) shout or curse angrily?					
2. Does (S) slam doors, kick furniture, and throw things?					
3. Does (S) attempt to hurt or hit others?					
4. Does (S) grab, push or scratch others?					
5. Is (S) unreasonably or uncharacteristically argumentative?					
6. Is (S) intrusive, such as taking others' possessions or entering another's room inappropriately?					
7. Is (S) in covert or open conflict with staff or others?					
8. Does (S) try to do things that are dangerous, such as lighting a match or climbing out a window?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

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E. Dysphoria

Does (S) seem sad or depressed? Does (S) say that he/she feels sad or depressed? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Careregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) have periods of tearfulness or sobbing that seem to indicate sadness?					
2. Does (S) say he/she is sad or in low spirits or acts as if he/she is sad or in low spirits?					
3. Does (S) put him/herself down or say that he/she feels like a failure?					
4. Does (S) seem very discouraged or say he/she has no future?					
5. Does (S) say he/she is a burden to the family and that the family would be better off without him/her?					
6. Does (S) express a wish for death or talk about killing him/herself?					
7. Does (S) say that he/she is a bad person and deserves to be punished?					
8. Does (S) have a worried or pained expression?					
9. Is (S) pessimistic or overly negative, expecting the worst?					
10. Is (S) suddenly irritable or easily annoyed?					
11. Has (S) changed in his/her eating habits, such as eating more/less or more/less often than usual?					
12. Does (S) talk about feeling guilty for things that for which he/she had no control over?					
13. Does (S) seem to no longer enjoy previously enjoyable activities?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

F. Anxiety:

Is (S) very nervous, worried, or frightened for no apparent reason? Does (S) seem very tense or fidgety? Is (S) afraid to be apart from you or from others that he/she trusts? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) say that he/she is worried about planned events such as appointments or family visits?					
2. Does (S) have periods of feeling shaky, unable to relax, or feeling very tense?					
3. Does (S) have periods of [or complain of] shortness of breath, gasping or sighing for no reason other than being nervous?					
4. Does (S) complain of butterflies in his/her stomach, or of racing or pounding of the heart because of being nervous [Symptoms not explained by ill health]?					
5. Does (S) avoid certain places or situations that make him/her more nervous such as meeting with friends or participating in ward activities?					
6. Does (S) become upset when separated from you? Does he/she cling to you to keep from being separated?					
7. Does (S) talk about feeling threatened or act as if he/she is frightened?					
8. Does (S) have a worried expression?					
9. Does (S) make repeated statements or comments about something bad that is going to happen?					
10. Does (S) express worry or concern over his/her health or body functions, worries that are not justified?					
11. Does (S) become tearful from worry					
12. Does (S) have unrealistic fears about being alone or being abandoned?					
13. Does (S) ask repeated questions about what he/she should be doing or where he/she should be going?					
14. Does (S) seem overly focused or concerned with tasks or activities and is not easily distracted or deterred?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

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G. Elation/Euphoria:

Does (S) seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if (S) has a persistent and abnormally good mood or finds humor where others do not.
(✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) appear to feel too good or act excessively happy?					
2. Does (S) find humor and laugh at things that others do not find funny?					
3. Does (S) seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)?					
4. Does (S) tell jokes or say things that are not funny to others but seem funny to him/her?					
5. Does (S) play childish games such as pinching or playing "keep away" for the fun of it?					
6. Does (S) "talk big" or claim to have more abilities or wealth than is true?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

H. Apathy/Indifference:

Has (S) lost interest in the world around him/her? Has (S) lost interest in doing things or lack motivation for starting new activities? Is (S) more difficult to engage in conversation or in doing chores? Is (S) apathetic or indifferent? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) seem less spontaneous and active than usual?					
2. Is (S) less likely to initiate a conversation?					
3. Is (S) less affectionate or lacking in emotions when compared to his/her usual self?					
4. Does (S) contribute less to household chores?					
5. Does (S) seem less interested in the activities and plans of others?					
6. Has (S) lost interest in friends and family members?					
7. Is (S) less enthusiastic about his/her usual interests?					
8. Does (S) sit quietly without paying attention to things going on around him/her?					
9. Has (S) reduced participation in social activities even when stimulated?					
10. Is (S) less interested in or curious about routine or new events in his/her environment?					
11. Does (S) express less emotion in response to positive or negative or events?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

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I. Disinhibition:

Does (S) seem to act impulsively without thinking? Does (S) do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) act impulsively without thinking of the consequences?					
2. Does (S) talk to total strangers as if he/she knew them?					
3. Does (S) say things to people that are insensitive or hurt their feelings?					
4. Does (S) say crude things or make inappropriate sexual remarks that they would not usually have said?					
5. Does (S) talk openly about very personal or private matters not usually discussed in public?					
6. Does (S) fondle, touch or hug others in a way that is improper and not appropriate and out of character for him/her?					
7. Does (S) dress or disrobe in inappropriate places or expose him/herself?					
8. Does (S) have a low tolerance for frustration or is impatient?					
9. Does (S) behave in way that is socially inappropriate for the situation, such as talking during a church service or singing at mealtime?					
10. Does (S) seem to lack social judgment about what to say or how to behave?					
11. Is (S) insulting to others?					
12. Does (S) seem unable/unwilling to control his/her eating?					
13. Does (S) seem aware but unconcerned about how his/her words or actions are affecting others?					
14. Does (S) go to the bathroom in inappropriate places (not due to incontinence?)					
15. Does (S) demand attention without regard to others?					
16. Does (S) take things from other?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

J. Irritability/Lability:

Does (S) get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks. We are interested in knowing if (S) has abnormal irritability, impatience or rapid emotional changes different from his/her usual self. (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) have a bad temper, flying "off the handle" easily over little things?					
2. Does (S) rapidly change moods from one to another, being fine one minute and angry the next?					
3. Does (S) have sudden flashes of anger?					
4. Is (S) impatient, having trouble coping with delays for waiting for planned activities?					
5. Is (S) cranky or irritable?					
6. Is (S) argumentative and difficult to get along with?					
7. Is (S) overly critical of others?					
8. Does (S) openly express conflict with friends, family and/or staff?					
9. Is (S) tearful or does he/she cry often and unpredictably?					
10. Does (S) have sudden changes of mood?					
11. Does (S) complain frequently?					
12. Has (S) stopped showing joy or enjoyment in response to usual day-to-day activities?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

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K. Aberrant Motor Disturbance:

Does (S) pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or things? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) pace or move in a wheelchair without apparent purpose?					
2. Does (S) rummage around opening and unpacking drawers and closets?					
3. Does (S) repeatedly put on and take off clothing?					
4. Does (S) have repetitive activities or "habits" that he/she performs over and over (e.g., wiping off the table, opening and closing doors)?					
5. Does (S) engage in repetitive activities such as handling buttons, picking, wrapping string, etc.?					
6. Does (S) fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot?					
7. Does (S) perform self-stimulating behaviors such as rocking, rubbing or moaning?					
8. Does (S) move with no rationale purpose, seemingly oblivious to his/her needs or safety?					
9. Are (S)'s movements and/or reactions slower than usual?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

L. Sleep Disorders:

Does (S) have difficulty sleeping (do not count present if (S) simply gets up once or twice per night to go to the bathroom and falls back asleep immediately). Is (S) up at night? Does (S) wander at night, get dressed, go into others' rooms? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) have difficulty falling asleep?					
2. Does (S) get up during the night? [do not count if (S) gets up once or twice per night only to go to the bathroom and falls back asleep immediately]					
3. Does (S) wander, pace or get involved in inappropriate activities at night?					
4. Does (S) awaken you during the night or disturb others?					
5. Does (S) awaken at night, dress, and plan to go out, thinking that it is morning and time to start the day?					
6. Does (S) sleep excessively during the day?					
7. Does (S) awaken too early in the morning (before other (S)s)?					
8. Is (S) agitated or concerned about sleeping at night? Does he/she worry about being able to fall asleep or about awakening at night?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

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M. Appetite and Eating Disorders:

Has (S) had any change in appetite, weight, or eating habits? (Count as NA if (S) is incapacitated and has to be fed.) Has there been any change in type of food he/she prefers? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Has (S) had a loss of appetite?					
2. Has (S) had an increase of appetite?					
3. Has (S) had a loss of weight?					
4. Has (S) had a gain of weight?					
5. Has (S) had a change in eating behavior such as putting too much food in his/her mouth at once?					
6. Has (S) had a change in the kind of food he/she likes, such as eating too many sweets or other specific types of food?					
7. Has (S) developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order?					
8. Does (S) eat or drink inappropriate substances or non-food items?					
9. Does (S) frequently demand food and/or drinks, even if he/she has just eaten/drank something?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

N. Aberrant Vocalizations:

Does (S) scream, talk excessively, or make strange noises? Does (S) have frequent verbal outbursts? (✓) Yes: ☐ No: ☐

Responses should be based on the past 4 weeks.	*Caregiver Interview**			*Patient Interview*	*Clinical Impression**
Description	*Frequency 0-4*	*Severity 0-3*	*Distress 0-5*	*Frequency 0-4*	*Severity 0-3*
1. Does (S) make strange noises, such as strange laughter or moaning?					
2. Does (S) scream, yell or moan loudly, apparently without reason?					
3. Does (S) talk excessively?					
4. Does (S) make repetitive requests or complaints?					
5. Is (S) verbally abusive or does he/she use lewd or threatening language?					
6. Does (S) make verbal sexual advances?					
7. Does (S) make frequent verbal outbursts?					
8. Does (S) participate in conversations with others, even if the conversation is nonsensical or difficult to understand?					
*Do not leave blank. Enter "0" if it does not occur.			**Column Total:**		

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Caregiver Questionnaire:

1. **What is your relationship to (S)?** _____
   1 = Spouse 2 = Sibling 3 = Child 4 = Grandchild 5 = Friend 6 = Parent 7 = paid caregiver
   99 = Other: _____

2. **How long have you known (S) (months and years)** _____?

3. **Where has (he/she) been living during the last 6 months?** _____

   1 = Home 2 = Assisted Living 3 = Nursing Home 9 = Other _____

4. **Are you currently living in the same household?** 0 = No 1 = Yes

   If yes, how many years have you been living in the same household? _____ 88 = Not Applicable 99 = Unknown

5. **How often did you interact with (S) during the last month?** _____

   1 = almost every day 2 = several times a week 3 = once a week 4 = 1-3 times a month 5 =< once a month 99 = Unknown

6. **Interviewer's Assessment of Respondent's Reliability as a Historian**

   0= Poor 1 = Fair 2 = Good 3 = Excellent

   Reason for interviewer's assessment:_____
   _____
   _____
   _____
   _____
   _____

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Interview Response Card

All responses pertain to behaviors that have occurred within the last month.

Frequency:
0=never
1=occasionally (<1/week)
2=often-about once1/week
3=frequently—several times a week but less than every day
4=very frequently—once or more/day

Severity/Intensity:
0=none
1=mild: produces little stress in (S)
2=moderate: distressing to (S) and cause substantial behavioral abnormalities
3=marked: a major source of behavioral abnormality

Caregiver Distress:
How emotionally distressing do you find (S) behavior?
0=not distressing
1=minimally
2=mildly
3=moderately
4=severely
5=extremely

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17.4.2. Dementia Apathy Interview and Rating (DAIR)

Not for ... for review on...

1) Does s/he tend to just sit and do nothing? Is this a change from how s/he was prior to the memory loss? 0 No Sits more -- *More apathetic* 1 Yes Sits less -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
2) Does s/he enjoy the things s/he can do as much as s/he used to before the illness began? Is this a change from how s/he was prior to the memory loss? 0 No Less enjoyment -- *More apathetic* 1 Yes More enjoyment -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
3) Will s/he start activities on her/his own? *(Examiner: This item refers to activities in general, however, if informant cannot think of any, insert as examples activities mentioned during initial querying of informant.)* Is this a change from how s/he was prior to the memory loss? 0 No Less likely to start -- *More apathetic* 1 Yes More likely to start -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
4) Does s/he suggest things to do for the day? Is this a change from how s/he was prior to the memory loss? 0 No Less likely to suggest -- *More apathetic* 1 Yes More likely to suggest -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate

5) Is s/he able to keep busy during the day?		0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always
Is this a change from how s/he was prior to the memory loss?	0 No	
Less able to keep busy -- *More apathetic*	1 Yes	
More able to keep busy -- *Less apathetic*	2 Yes	
		9 Unable to rate
6) Does s/he start conversations?		0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always
Is this a change from how s/he was prior to the memory loss?	0 No	
Less likely to start -- *More apathetic*	1 Yes	
More likely to start -- *Less apathetic*	2 Yes	
		9 Unable to rate
7) Is s/he concerned about how other people feel?		0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always
Is this a change from how s/he was prior to the memory loss?	0 No	
Less concerned -- *More apathetic*	1 Yes	
More concerned -- *Less apathetic*	2 Yes	
		9 Unable to rate
8) Are there things that s/he is enthusiastic about?		0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always
Is this a change from how s/he was prior to the memory loss?	0 No	
Less enthusiastic -- *More apathetic*	1 Yes	
More enthusiastic -- *Less apathetic*	2 Yes	
		9 Unable to rate
9) Does s/he seem to care less about finishing things that s/he has started?		0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always
Is this a change from how s/he was prior to the memory loss?	0 No	
Cares less about finishing -- *More apathetic*	1 Yes	
Cares more about finishing -- *Less apathetic*	2 Yes	
		9 Unable to rate

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10) Does it seem important to her/him to succeed in the things s/he tries to do? Is this a change from how s/he was prior to the memory loss? 0 No Less important to succeed -- *More apathetic* 1 Yes More important to succeed -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
11) Does s/he no longer seem to react to things as much as s/he used to prior to the illness? Is this a change from how s/he was prior to the memory loss? 0 No Less reactive -- *More apathetic* 1 Yes More reactive -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
12) Is s/he less spontaneous? Is this a change from how s/he was prior to the memory loss? 0 No Less spontaneous-- *More apathetic* 1 Yes More spontaneous -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
13) Does s/he seem indifferent to what's going on around her/him? Is this a change from how s/he was prior to the memory loss? 0 No More indifferent -- *More apathetic* 1 Yes Less indifferent -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
14) Does s/he seem less active? Is this a change from how s/he was prior to the memory loss? 0 No Less active -- *More apathetic* 1 Yes More active -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate

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15) Does s/he show a full range of emotions (that is, s/he is able to feel happy, angry, sad, worried)? Is this a change from how s/he was prior to the memory loss? 0 No Flat affect -- *More apathetic* 1 Yes Better range of emotions -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate
16) Does s/he show interest in news about friends and relatives? Is this a change from how s/he was prior to the memory loss? 0 No Less interested -- *More apathetic* 1 Yes More interested -- *Less apathetic* 2 Yes	0 No, almost never 1 Yes, occasionally 2 Yes, often 3 Yes, almost always 9 Unable to rate

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17.4.3. Apathy Evaluation Scale-Clinician (AES-C)

Apathy Evaluation Scale (Clinician Version; AES-C)

Name: _____ Date:____/____/____

Rater: _____

Rate each item based on an interview of the subject. The interview should begin with a description of the subject=s interests, activities and daily routine. Base your ratings on both verbal and non-verbal information. Ratings should be based on the past 4 weeks. For each item ratings should be judged:

Not at All Characteristic 1	Slightly Characteristic 2	Somewhat Characteristic 3	A Lot Characteristic 4

__	1.	S/he is interested in things.	+ C Q*
__	2.	S/he gets things done during the day.	+ B Q
__	3.	Getting things started on his/her own is important to him/her.	+ C SE
__	4.	S/he is interested in having new experiences.	+ C Q
__	5.	S/he is interested in learning new things.	+ C Q
__	6.	S/he puts little effort into anything	- B
__	7.	S/he approaches life with intensity.	+ E
__	8.	Seeing a job through to the end is important to her/him.	+ C SE
__	9.	S/he spends time doing things that interest her/him.	+ B
___	10.	Someone has to tell her/him what to do each day.	- B
__	11.	S/he is less concerned about her/his problems than s/he should be	- C
__	12.	S/he has friends.	+ B Q
__	13.	Getting together with friends is important to him/her.	+ C SE
__	14.	When something good happens, s/he gets excited.	+ E
__	15.	S/he has an accurate understanding of her/his problems.	+ O
__	16.	Getting things done during the day is important to her/him.	+ C SE
__	17.	S/he has initiative.	+ O
__	18.	S/he has motivation.	+ O

The Apathy Evaluation scale was developed by Robert S. Marin, M.D. Development and validation studies are described in Marin, R.S., Biedrzycki, R.C., Firinciogullari, S. Reliability and Validity of the Apathy Evaluation Scale, Psychiatry Research, 38:143-162, 1991

*Note: Items that have positive versus negative syntax are identified by +/-. Type of item: C = cognitive; B = behavior; E = emotional; O = other. The definitions of self-evaluation (SE) items and quantifiable items (Q) are discussed in the administrations guidelines (available upon request from marinr@upmc.edu).

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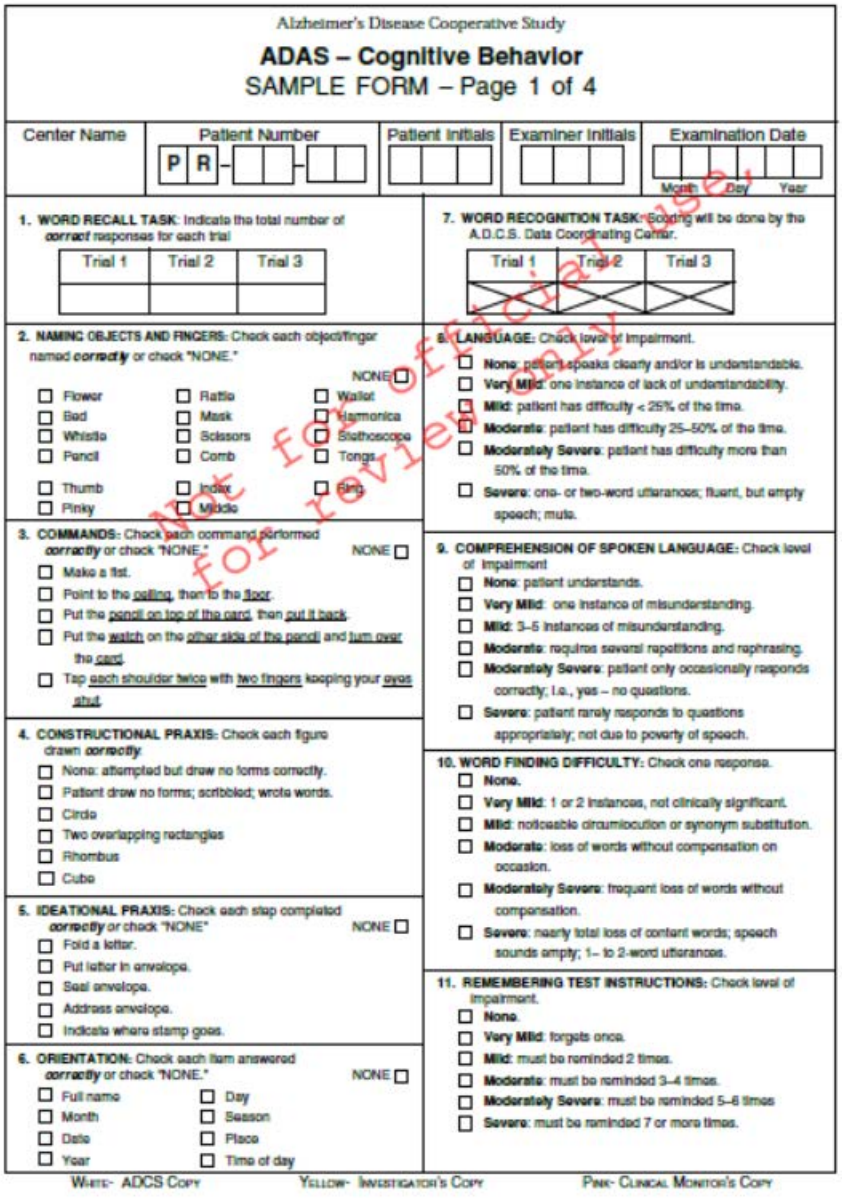
17.4.4. Alzheimer's Disease Assessment Scale – Cognition Subscale (ADAS-Cog)



Alzheimer's Disease Cooperative Study

ADAS – Cognitive Behavior

SAMPLE FORM – Page 1 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R – –			Month Day Year

1. WORD RECALL TASK: Indicate the total number of *correct* responses for each trial

Trial 1	Trial 2	Trial 3

2. NAMING OBJECTS AND FINGERS: Check each object/finger named *correctly* or check "NONE."

NONE ☐

☐ Flower	☐ Rattle	☐ Wallet
☐ Bed	☐ Mask	☐ Harmonica
☐ Whistle	☐ Scissors	☐ Stethoscope
☐ Pencil	☐ Comb	☐ Tongs
☐ Thumb	☐ Index	☐ Ring
☐ Pinky	☐ Middle	

3. COMMANDS: Check each command performed *correctly* or check "NONE."

NONE ☐

- ☐ Make a fist.
- ☐ Point to the ceiling, then to the floor.
- ☐ Put the pencil on top of the card, then put it back.
- ☐ Put the watch on the other side of the pencil and turn over the card.
- ☐ Tap each shoulder twice with two fingers keeping your eyes shut.

4. CONSTRUCTIONAL PRAXIS: Check each figure drawn *correctly*.

- ☐ None: attempted but drew no forms correctly.
- ☐ Patient drew no forms; scribbled; wrote words.
- ☐ Circle
- ☐ Two overlapping rectangles
- ☐ Rhombus
- ☐ Cube

5. IDEATIONAL PRAXIS: Check each step completed *correctly* or check "NONE"

NONE ☐

- ☐ Fold a letter.
- ☐ Put letter in envelope.
- ☐ Seal envelope.
- ☐ Address envelope.
- ☐ Indicate where stamp goes.

6. ORIENTATION: Check each item answered *correctly* or check "NONE."

NONE ☐

☐ Full name	☐ Day
☐ Month	☐ Season
☐ Date	☐ Place
☐ Year	☐ Time of day

7. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.

Trial 1	Trial 2	Trial 3

8. LANGUAGE: Check level of impairment.

- ☐ **None**: patient speaks clearly and/or is understandable.
- ☐ **Very Mild**: one instance of lack of understandability.
- ☐ **Mild**: patient has difficulty < 25% of the time.
- ☐ **Moderate**: patient has difficulty 25–50% of the time.
- ☐ **Moderately Severe**: patient has difficulty more than 50% of the time.
- ☐ **Severe**: one- or two-word utterances; fluent, but empty speech; mute.

9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment

- ☐ **None**: patient understands.
- ☐ **Very Mild**: one instance of misunderstanding.
- ☐ **Mild**: 3–5 instances of misunderstanding.
- ☐ **Moderate**: requires several repetitions and rephrasing.
- ☐ **Moderately Severe**: patient only occasionally responds correctly; i.e., yes – no questions.
- ☐ **Severe**: patient rarely responds to questions appropriately; not due to poverty of speech.

10. WORD FINDING DIFFICULTY: Check one response.

- ☐ **None.**
- ☐ **Very Mild**: 1 or 2 instances, not clinically significant.
- ☐ **Mild**: noticeable circumlocution or synonym substitution.
- ☐ **Moderate**: loss of words without compensation on occasion.
- ☐ **Moderately Severe**: frequent loss of words without compensation.
- ☐ **Severe**: nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.

11. REMEMBERING TEST INSTRUCTIONS: Check level of impairment.

- ☐ **None.**
- ☐ **Very Mild**: forgets once.
- ☐ **Mild**: must be reminded 2 times.
- ☐ **Moderate**: must be reminded 3–4 times.
- ☐ **Moderately Severe**: must be reminded 5–6 times
- ☐ **Severe**: must be reminded 7 or more times.

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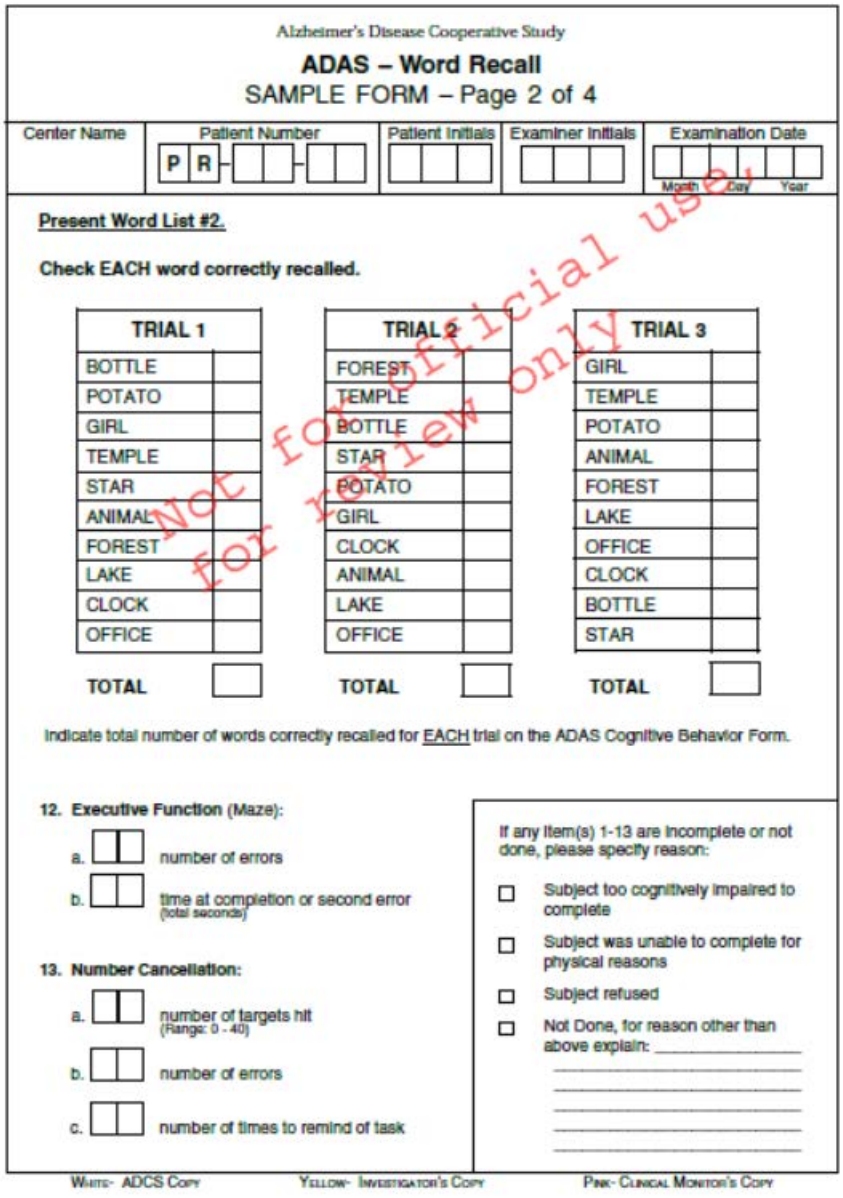

Alzheimer's Disease Cooperative Study

ADAS – Word Recall

SAMPLE FORM – Page 2 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R - -			Month Day Year

Present Word List #2.

Check EACH word correctly recalled.

TRIAL 1		TRIAL 2		TRIAL 3	
BOTTLE		FOREST		GIRL	
POTATO		TEMPLE		TEMPLE	
GIRL		BOTTLE		POTATO	
TEMPLE		STAR		ANIMAL	
STAR		POTATO		FOREST	
ANIMAL		GIRL		LAKE	
FOREST		CLOCK		OFFICE	
LAKE		ANIMAL		CLOCK	
CLOCK		LAKE		BOTTLE	
OFFICE		OFFICE		STAR	
TOTAL		**TOTAL**		**TOTAL**	

Indicate total number of words correctly recalled for EACH trial on the ADAS Cognitive Behavior Form.

12. Executive Function (Maze):

a. ☐☐ number of errors

b. ☐☐ time at completion or second error (total seconds)

13. Number Cancellation:

a. ☐☐ number of targets hit (Range: 0 - 40)

b. ☐☐ number of errors

c. ☐☐ number of times to remind of task

If any item(s) 1-13 are incomplete or not done, please specify reason:

- ☐ Subject too cognitively impaired to complete
- ☐ Subject was unable to complete for physical reasons
- ☐ Subject refused
- ☐ Not Done, for reason other than above explain: _____

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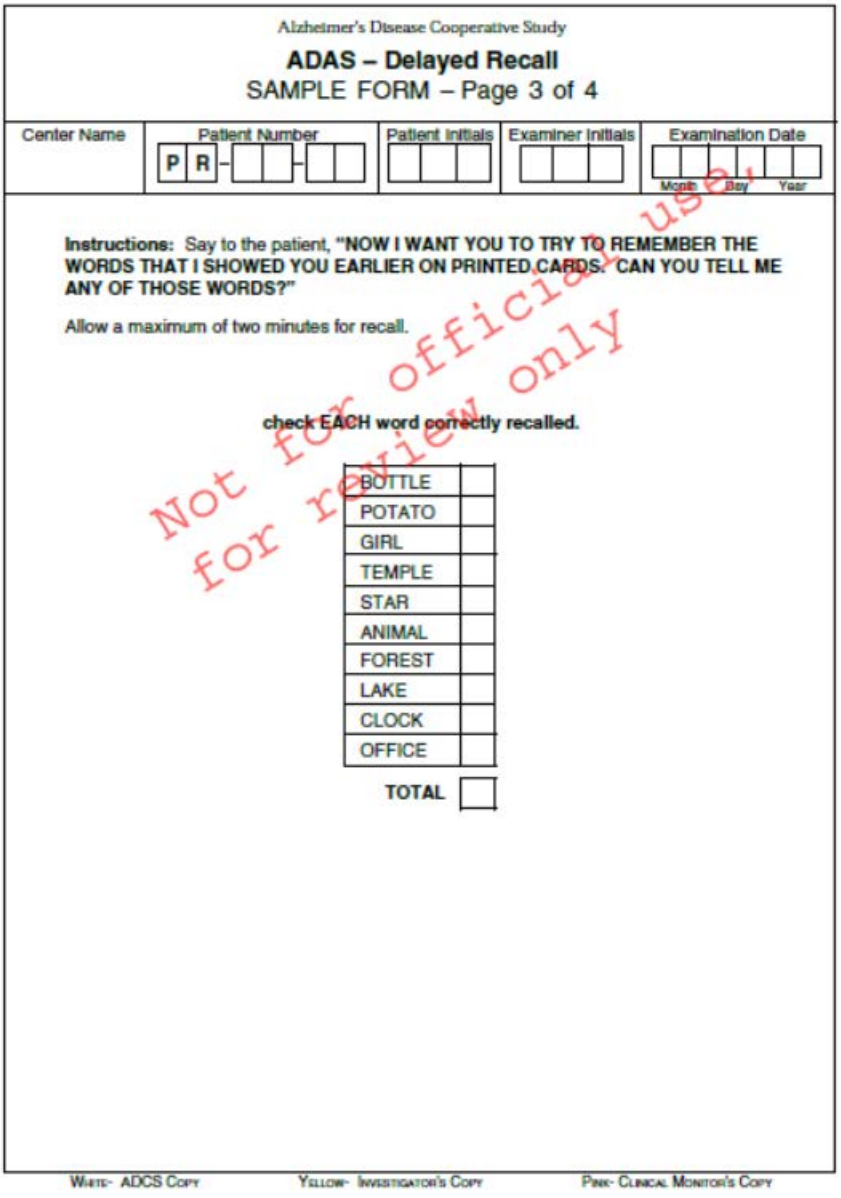

Alzheimer's Disease Cooperative Study

ADAS – Delayed Recall

SAMPLE FORM – Page 3 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R - - -			Month Day Year

Instructions: Say to the patient, **"NOW I WANT YOU TO TRY TO REMEMBER THE WORDS THAT I SHOWED YOU EARLIER ON PRINTED CARDS. CAN YOU TELL ME ANY OF THOSE WORDS?"**

Allow a maximum of two minutes for recall.

check EACH word correctly recalled.

BOTTLE	
POTATO	
GIRL	
TEMPLE	
STAR	
ANIMAL	
FOREST	
LAKE	
CLOCK	
OFFICE	
TOTAL	

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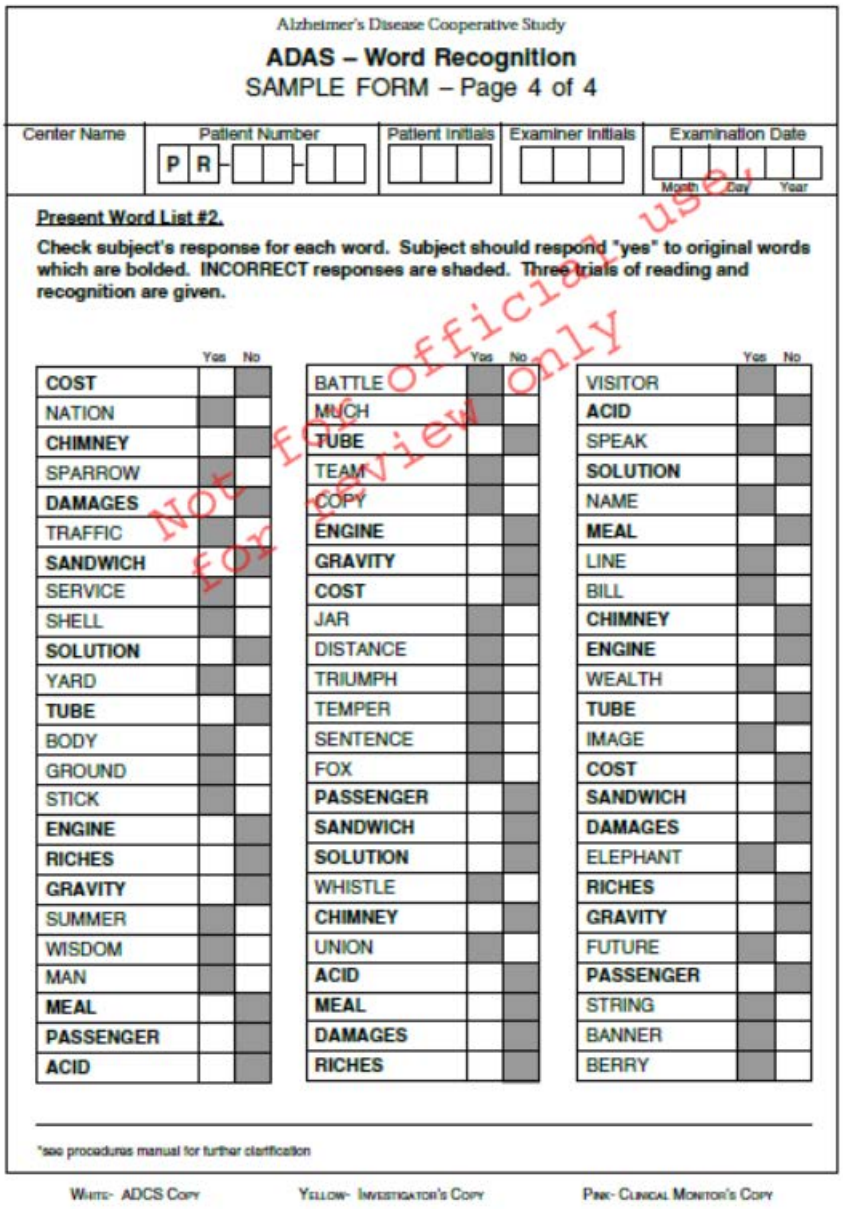

Alzheimer's Disease Cooperative Study

ADAS – Word Recognition

SAMPLE FORM – Page 4 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R - -			Month Day Year

Present Word List #2.

Check subject's response for each word. Subject should respond "yes" to original words which are bolded. INCORRECT responses are shaded. Three trials of reading and recognition are given.

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	Yes	No
COST		
NATION		
CHIMNEY		
SPARROW		
DAMAGES		
TRAFFIC		
SANDWICH		
SERVICE		
SHELL		
SOLUTION		
YARD		
TUBE		
BODY		
GROUND		
STICK		
ENGINE		
RICHES		
GRAVITY		
SUMMER		
WISDOM		
MAN		
MEAL		
PASSENGER		
ACID		

	Yes	No
BATTLE		
MUCH		
TUBE		
TEAM		
COPY		
ENGINE		
GRAVITY		
COST		
JAR		
DISTANCE		
TRIUMPH		
TEMPER		
SENTENCE		
FOX		
PASSENGER		
SANDWICH		
SOLUTION		
WHISTLE		
CHIMNEY		
UNION		
ACID		
MEAL		
DAMAGES		
RICHES		

	Yes	No
VISITOR		
ACID		
SPEAK		
SOLUTION		
NAME		
MEAL		
LINE		
BILL		
CHIMNEY		
ENGINE		
WEALTH		
TUBE		
IMAGE		
COST		
SANDWICH		
DAMAGES		
ELEPHANT		
RICHES		
GRAVITY		
FUTURE		
PASSENGER		
STRING		
BANNER		
BERRY		

*see procedures manual for further clarification

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17.4.5. Modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (mADCS-CGIC) (example pages from caregiver subsequent visit only)

CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET

Specify completion date: _____

ADCS - CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET
Subsequent Visit CGIC Evaluation of Caregiver Interview

Time of day interview started: _____ (24 hour clock)

Brief Instructions: See Instruction sheet. Use this form to record information for making a CGIC rating after interviewing caregiver. You may refer only to the Baseline Evaluation form. A brief clinical assessment of mental state should be made. No particularformat or order is suggested for the interview.

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Area	Probes	Caregiver's Notes
Relevant history	• clinical events since baseline: changes? illnesses?	
Observation/ Evaluation	• appearance	
MENTAL/COGNITIVE STATE [Structured exam, if used: _____]		
Arousal/ Alertness/ Attention/ Concentration	• confusion/clarity • excitement/reactivity • state of consciousness	

CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET

Area	Probes	Caregiver's Notes
Orientation	• time • place • person • time relationships • travel • find his/her way • recognizes self/others/objects • reacts appropriately	
Memory	• registration • recall • long term/remote • recall for past events	
Language/Speech	• fluency/ expressive language receptive language • comprehension • paraphasia/word finding • naming, amount • repetition • follows directions	
Praxis	• constructional ability • ideational praxis • ideomotor/imitation	

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CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET

Area	Probes	Caregiver's Notes
Judgment/ Problem solving/ Insight	• patient's behavior in situations requiring judgment	
BEHAVIOR		
Thought content	• organization • appropriateness • hostile expression	
Hallucinations/ Delusions/ Illusions	• auditory/visual • misperceptions • systematized/developed	
Behavior/Mood	• affect/lability • unusual/bizarre • uninhibited/sexually inappropriate • motivation/energy • wandering/getting lost • agitation/aggression • hostility • depression-related • anxiety-related • appropriateness • cooperativeness • demanding/dependent	

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CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET

Area	Probes	Caregiver's Notes
Sleep/Appetite	• sleep disorder • insomnia (type?) • nocturnal activity • hyper-, hyposomnia • appetite/weight change	
Neurological/ Psychomotor activity	• overall motor activity • posture/gait • movement disorder • unusual motor behavior • daily patterns • pacing	
FUNCTIONING		
Basic and complex (instrumental) functional ability	• mobility • hygiene/grooming • dressing • self-feeding • shopping • household chores/hobbies • finances • driving	
Social function	• participation in: social interactions community activites • independence • helplessness	

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CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET		
Area	Probes	Caregiver's Notes
Apathy: Diminished Initiative	- Initiate conversation or tasks - Amount of effort - Get things done during the day	
Apathy: Diminished Interest	- Concerns about their problems - Interest in family / friends / new things / experiences - Approaches life with intensity	
Apathy: Emotional blunting	- Affectionate - Express emotions - Excited when good things happen	

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CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET

Notes, comments, summary statement:

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Information from other sources:

Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483). Schneider, L.; Olin, J.; Doody, R.; Clark, C.; Morris, J.; Reisberg, B.; Schmitt, F.; Grundman, M.; Thomas, R.; Ferris, S.; and the ADCS. "Validity and Reliability of the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change." *Alzheimer's Disease and Associated Disorders*, 1997. Vol 11(2): S22-S32.

CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET

Compared with the patient's condition at Baseline, how would you rate the current state of the patient's apathy?

- ☐ Marked improvement
- ☐ Moderate improvement
- ☐ Minimal improvement
- ☐ No change
- ☐ Minimal worsening
- ☐ Moderate worsening
- ☐ Marked worsening

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CLINICAL GLOBAL IMPRESSION OF CHANGE WORKSHEET

Compared with the patient's condition at Baseline, how would you rate the patient's current overall clinical status?

- ☐ Marked improvement
- ☐ Moderate improvement
- ☐ Minimal improvement
- ☐ No change
- ☐ Minimal worsening
- ☐ Moderate worsening
- ☐ Marked worsening

17.4.6. Modified Clinical Global Impression-Severity Scale (mCGI-S)

Modified Clinician Global Impression – Severity Scale (mCGI-S)

1. **Apathy Symptom Severity**

Considering your total clinical experience with this particular population, how severe do you judge the patient's level of ***apathy*** at this time?

This rating is based upon observed and reported symptoms, behavior, and function in the past four weeks. Clearly, symptoms and behavior can fluctuate over time; the score should reflect the average severity level across these four weeks (including today).

Please rate on the following seven-point scale:

1 = no symptoms

2 = borderline symptoms

3 = mild symptoms

4 = moderate symptoms

5 = marked symptoms

6 = severe symptoms

7 = very severe symptoms

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2. **Dementing Illness- Overall Condition Severity**

Considering your total clinical experience with this particular population, how ill is the subject at this time with respect to the overall condition of their dementing illness?

This rating is based upon observed and reported symptoms, behavior, and function in the past four weeks. Clearly, symptoms and behavior can fluctuate over time; the score should reflect the average severity level across these four weeks (including today).

Please rate on the following seven-point scale:

1 = normal, not at all ill

2 = borderline ill

3 = mildly ill

4 = moderately ill

5 = markedly ill

6 = severely ill

7 = among the most extremely ill patients

17.4.7. Caregiver Global Impression-Severity Scale (CaGI-S)

CaGI- Version 02.18.2021

CAREGIVER GLOBAL IMPRESSION SCALES OF SEVERITY AND CHANGE FROM BASELINE FOR APATHY SYMPTOMS AND OVERALL DEMENTING ILLNESS

Directions for Administration

Part 1: Apathy Ratings

1. **Caregiver Global Impression – Severity of apathy symptoms** over the past 4 weeks

Rater hands to the patient's caregiver a laminated card (card 1; side 1) with the apathy definitions and ratings listed below.

Read definition of apathy and question / responses out loud to the caregiver and direct them to review the laminated card.

"I am going to ask you some questions about the patient's symptoms of apathy. By apathy we mean:"

APATHY

- Diminished initiative or independence in starting activities
  Such as hobbies, chores, self-care, conversation
- Diminished interest or enthusiasm about usual activities
  Such as social events with family & friends or decreased participation in activities or completion of activities.
- Diminished emotional responsiveness
  Such as decreased affection, expression of feelings, or concern about others' feelings

"Please rate the severity of the patient's symptoms of apathy during the past 4 weeks including today."

*1 = **normal:** no symptoms of apathy.*

*2 = **borderline apathy:** some decreased initiative or enthusiasm for usual enjoyed activities has occurred on some limited occasions in the last 4 weeks but it has not interfered with daily routines.*

*3 = **mild apathy:** apathy has been notable but patient responds to suggestions to engage in activities.*

*4 = **moderate apathy:** apathy is evident on a consistent daily basis and is only overcome through coaxing and encouragement.*

*5 = **marked apathy:** apathy is very evident. It is persistent and responds only to continual encouragement or powerful events such as visits from close relatives or family members.*

*6 = **severe apathy:** apathy is very evident and usually fails to respond to any encouragement or external events.*

*7 = **extremely severe apathy:** the patient is very disengaged and responds infrequently to encouragement or external events.*

Rater Notes:_____

_____

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CaGI- Version 02.18.2021

Part 2: Dementia Ratings

1. **Caregiver Global Impression – Severity of overall dementing illness** over the past 4 weeks

Rater hands Card 2 to the Caregiver with Side 1 facing up revealing rating language for dementia, and says:

"Considering your total experience in caring for the patient, how would you rate the overall severity of their dementing illness during the past 4 weeks including today. By dementing illness, we mean the total disease: the memory & cognitive disorder, impairment in daily function, and their apathy as well as any other behaviors."

*1 = **normal**, not at all impaired.*

*2 = **borderline ill** – subtle symptoms that do not interfere significantly with daily life.*

*3 = **mildly ill** – the dementia interferes with independence in daily functions outside the home, but the patient is still able to engage in community activities and home responsibilities.*

*4 = **moderately ill**- there is no pretense of independence outside the home. The patient requires help with more complex home activities but is still able to do routine chores and self-care.*

*5 = **markedly ill**- the patient is able to complete only very simple chores and may require some assistance or prompting with their self-care.*

*6 = **severely ill**- the patient is not able to execute simple chores and is dependent in many aspects of their self-care.*

*7 = **extremely severely ill**- the patient is completely dependent on others for their self-care.*

Rater Notes:_____

_____

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17.4.8. Caregiver Global Impression-Change Scale (CaGI-C)

CaGI- Version 02.18.2021

Caregiver Global Impression – Change in apathy symptoms since the beginning of the study.
Rater flips over card 1 to side 2 revealing the apathy definition and change anchors listed below.

Read definition of apathy and question / responses out loud to the caregiver and direct them to review the laminated card. If you are confident that the caregiver recalls the definition of apathy from the previous question, the definition does not need to be read aloud.

"As a reminder, by apathy we mean:"

APATHY

- Diminished initiative or independence in starting activities
  Such as hobbies, chores, self-care, conversation
- Diminished interest or enthusiasm about usual activities
  Such as social events with family & friends or decreased participation in activities or completion of activities.
- Diminished emotional responsiveness
  Such as decreased affection, expression of feelings, or concern about others' feelings

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"Overall, how have the patient's symptoms of apathy changed (if at all) since the beginning of the study (e.g., before the person started treatment)?"

1 = marked improvement in apathy

2 = moderate improvement in apathy

3 = minimal improvement in apathy

4 = no change in apathy

5 = minimal worsening in apathy

6 = moderate worsening in apathy

7 = marked worsening in apathy

Rater Notes:_____

_____

CaGI- Version 02.18.2021

2. **Caregiver Global Impression - Change in overall dementing illness** since the beginning of the study

Rater flips over Card 2 (card 2; side 2) revealing the apathy change anchors and says:

*"Considering your total experience in caring for the patient, how has their dementing illness **changed (if at all)** since the beginning of the study (e.g., before the person started treatment)?"*

1 = marked improvement in overall dementia

2 = moderate improvement in overall dementia

3 = minimal improvement in overall dementia

4 = no change in overall dementia

5 = minimal worsening in overall dementia

6 = moderate worsening in overall dementia

7 = marked worsening in overall dementia

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Rater Notes:_____

_____

17.5. Prohibited Prior Medications

Prohibited Prior Medications	Prohibited Duration of Use Prior to Randomization
Cholinesterase inhibitors and memantine are prohibited with the following exception: • Dose has been stable for 60 days prior to randomization	30 days (unless dose stable for 60 days prior to randomization)
Antipsychotics	3 months
Tricyclic antidepressants and bupropion	30 days
SSRI/SNRIs (other than trazodone) are prohibited with the following exceptions: • Dose has been stable for 60 days prior to randomization	30 days (unless dose stable for 60 days prior to randomization)
Trazodone >50 mg/day for the treatment of depression.	30 days
Mood stabilizers and anticonvulsants (eg, lithium, valproate, carbamazepine)	30 days
Pregabalin and gabapentin are prohibited with the following exceptions: • Dose has been stable for 60 days prior to randomization • Medication is being used for pain indication. Usage for other indications (eg, behavioral management) is not allowed during the trial. • Dose should not exceed the recommended doses as listed in the respective US Package Inserts Dosage and Administration sections, including the maximum recommended dose in subgroup populations (as applicable)	30 days (unless dose stable for 60 days prior to randomization)
Benzodiazepines	30 days
Opioid analgesics	30 days
High CNS penetrant anticholinergics used to treat tremor, other movement disorders, and overactive bladder (eg, benzatropine, oxybutynin, solifenacin, tolterodine). Low CNS penetrant anticholinergics used to treat overactive bladder (eg, trospium) are allowed provided the dose does not exceed the maximum recommended doses as listed in the respective US Package Inserts Dosage and Administration sections, including the maximum recommended dose in subgroup populations (as applicable; eg, patients greater than 60 years of age).	30 days
Atomoxetine, modafinil, armodafinil, and varenicline	30 days
Psychostimulants (eg, methylphenidate, amphetamine, lisdexamfetamine)	30 days
Levodopa and/or other dopamine agonists (including levodopa inhalation powder or apomorphine)	7 days
Nutritional supplements and nonprescription herbal preparations with known CNS effects (eg, St. John's wort, omega-3 fatty acids, kava extracts, GABA supplements) that are provided in a medicinal form (eg, pill, capsule)	30 days

Prohibited Prior Medications	Prohibited Duration of Use Prior to Randomization
Strong or moderate inducers or inhibitors of CYP3A4 metabolism	Inhibitors: 5 half-lives or 30 days (shorter of the 2) Inducers: 5 half-lives or 21 days (longer of the 2)
Any investigational agent	60 days or 5 half-lives (longer of the 2)

Abbreviations: CNS=central nervous system; CYP=cytochrome P450; GABA=gamma-aminobutyric acid; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; US=United States.

17.6. Prohibited Concomitant Medications

Prohibited Concomitant Medications	
1.	Cholinesterase inhibitors and memantine are prohibited with the following exception: • Dose was stable for 60 days prior to randomization and subject remains on the same dose throughout the duration of treatment
2.	All antipsychotics
3.	Tricyclic antidepressants and bupropion are prohibited • SSRI and SNRI antidepressants are allowed provided the following: o The dose has been stable for 60 days prior to randomization and expected to remain unchanged for the duration of the trial.
4.	Trazodone >50 mg/day for the treatment of depression
5.	Mood stabilizers and anticonvulsants (eg, lithium, valproate, carbamazepine)
6.	Pregabalin and gabapentin are prohibited with the following exceptions: • Dose has been stable for 60 days prior to randomization • Medication is being used for pain indication. Usage for other indications (eg, behavioral management) is not allowed during the trial. • Dose should not exceed the recommended doses as listed in the respective US Package Inserts Dosage and Administration sections, including the maximum recommdned dose in subgroup populations (as applicable)
7.	Benzodiazepines and buspirone are prohibited • Nonbenzodiazepine sleep agents (ie, zolpidem, zaleplon, zopiclone, and eszopiclone) and low-dose trazodone (up to 50 mg) are allowed for treatment of insomnia o For the nonbenzodiazepine sleep aids, only one of the listed medications may be used. Country-specific prescribing information must be followed to determine the maximum allowable daily dose for the treatment of insomnia in elderly or debilitated patients (typically half of the normal adult maximum dose).
8.	Opioid analgesics
9.	High CNS penetrant anticholinergics used to treat tremor, other movement disorders, and overactive bladder (eg, benzatropine, oxybutynin, solifenacin, tolterodine). • Low CNS penetrant anticholinergics used to treat overactive bladder (eg, trospium) are allowed provided the dose does not exceed the maximum recommended doses as listed in the respective US Package Inserts Dosage and Administration sections, including the maximum recommended dose in subgroup populations (as applicable; eg, patients greater than 60 years of age).
10.	Atomoxetine, modafinil, armodafinil, and varenicline
11.	Psychostimulants (eg, methylphenidate, amphetamine, lisdexamfetamine)
12.	Antihistamines with sedating effects (eg, diphenhydramine) • Nonsedating antihistamines (eg, fexofenadine, loratadine) are allowed
13.	Anticoagulants such as warfarin, heparin, direct thrombin inhibitors (eg, dabigatran), and direct factor Xa inhibitors (eg, rivaroxaban, apixaban). • Anti-platelet medications (eg, aspirin, clopidogrel) are permitted.

Prohibited Concomitant Medications	
14.	Levodopa and/or other dopamine agonists (including levodopa inhalation powder or apomorphine)
15.	Nutritional supplements and nonprescription herbal preparations (eg, St. John's wort, kava extracts, GABA supplements) that are provided in a medicinal form (eg, pill, capsule) due to the potential for CYP3A4 drug-drug interactions
16.	Strong or moderate inducers or inhibitors of CYP3A4 metabolism (see Protocol Appendix 6)
17.	Any investigational agent

Abbreviations: CNS=central nervous system; CYP=cytochrome P450; GABA=gamma-aminobutyric acid; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; US=United States.

17.7. Schedule of Assessment

Table 4: Schedule of Assessments

Trial Period	**Screening Period[a,b]**	**Treatment Period (12 weeks)**									**Post-treatment Follow-up (4 weeks)**	
Visit/Contact[c]	**Visit 1**	**Visit 2/ Baseline**	**Visit 3[d]**	**Contact**	**Visit 4[e]**	**Contact**	**Visit 5**	**Contact**	**Contact**	**Visit 6/ ET[f]**	**Visit 7**	**Con-tact**
Trial Day	**-31 to -1**	**1**	**8**	**14[g]/18**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**
Trial Week			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
Window			**±3 days**			**±5 days**						
Entrance and History												
Informed consent[h]	X											
Assign subject number	X											
Eligibility criteria	X	X										
Medical and psychiatric history	X											
Demography	X											
History of drug and alcohol use	X											
DCA (electronic form)[i]	X											
MMSE (electronic form)[i]	X											
Randomization		X										
Pharmacodynamic and Other Endpoint Assessments												
Electronic Forms[i]												
NPI	X	X					X			X		
NPI-C (apathy only)		X					X			X		

Trial Period	**Screening Period[a,b]**	**Treatment Period (12 weeks)**									**Post-treatment Follow-up (4 weeks)**	
Visit/Contact[c]	**Visit 1**	**Visit 2/ Baseline**	**Visit 3[d]**	**Contact**	**Visit 4[e]**	**Contact**	**Visit 5**	**Contact**	**Contact**	**Visit 6/ ET[f]**	**Visit 7**	**Con-tact**
Trial Day	**-31 to -1**	**1**	**8**	**14[g]/18**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**
Trial Week			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
Window			**±3 days**			**±5 days**						
NPI-C (dysphoria)		X					X			X		
DAIR		X					X			X		
AES-C		X					X			X		
ADAS-Cog13		X								X		
mADCS-CGIC worksheet		X										
mADCS-CGIC[j]							X			X		
mCGI-S		X					X			X		
CaGI-S		X					X			X		
CaGI-C[j]							X			X		
Safety Assessments												
Physical/ neurological examination[k]	X									X		
ECG[l]	X	X	X		X		X			X	X	
Vital sign measurements[m]	X	X	X		X		X			X	X	
C-SSRS[n](electronic form)[i]	X	X	X		X		X			X	X	
Prior/concomitant treatments[o]	←----------→											
Adverse event monitoring[o]	←----------→											

Trial Period	Screening Period[a,b]	Treatment Period (12 weeks)									Post-treatment Follow-up (4 weeks)	
Visit/Contact[c]	**Visit 1**	**Visit 2/ Baseline**	**Visit 3[d]**	**Contact**	**Visit 4[e]**	**Contact**	**Visit 5**	**Contact**	**Contact**	**Visit 6/ ET[f]**	**Visit 7**	**Con-tact**
Trial Day	**-31 to -1**	**1**	**8**	**14[g]/18**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**
Trial Week			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
Window			**±3 days**			**±5 days**						
Laboratory												
Blood for safety laboratory sample	X	X	X		X		X			X	X	
Urine for safety laboratory[p]	X	X	X		X		X			X		
Prolactin level[q]		X								X		
Urine drug screening[r]	X											
Test for alcohol	X	X										
Hepatitis B, C, HIV	X											
PK blood sample[s]			X		X		X			X		
Blood collection for COMT genotyping[t]		X										
Blood samples for future biospecimen research[u]		X										
Other												
IMP dispensing[v]		X	X		X		X					
IMP compliance assessment[v]			X	X	X	X	X	X	X	X		

Abbreviations: AD=Alzheimer's disease; ADAS-Cog13=Alzheimer's Disease Assessment Scale – Cognition 13-item scale; AES-C=Apathy Evaluation Scale-Clinician; CaGI-C=Caregiver Global Impression–Change Scale; CaGI-S=Caregiver Global Impression–Severity Scale; COMT=catechol-O-methyltransferase; COVID-19=coronavirus disease-2019; C-SSRS=Columbia-Suicide Severity Rating Scale; DAIR=Dementia Apathy Interview and Rating; DCA=diagnostic criteria for apathy; DLB=dementia with Lewy bodies; ECG=electrocardiogram; eCRF=electronic case report form; ET=early termination; FTD=frontotemporal dementia; HIV=human immunodeficiency virus; IMP=investigational medicinal product; IRT=interactive response technology; mADCS-CGIC=modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; mCGI-S=modified Clinical Global Impression–Severity Scale; MMSE=Mini-

Mental State Examination; NPI=Neuropsychiatric Inventory; NPI-C=Neuropsychiatric Inventory-Clinician; PK=pharmacokinetic(s); SARS-CoV2=severe acute respiratory syndrome coronavirus 2; VAD=vascular dementia.

a. Extension of screening may be allowed following discussion and documented approval by the medical monitor prior to the expiration of the Screening Period. Extension will only be granted in rare circumstances and the 30-day duration should be adhered to whenever possible.
b. Individual sites may require subjects to have SARS-CoV2 testing done prior to randomization. SARS-CoV2 testing may be performed any time after randomization per the investigator's discretion.
c. Contact with subject via phone call, internet/web, or other acceptable means of communication to check on their status.
d. Subjects will be monitored during scheduled assessments following dosing and those who do not tolerate the increase to Step 3 dose may decrease back down to Step 2 dose.
e. Subjects will be monitored during scheduled assessments following dosing and those who do not tolerate the increase to Step 5 dose may decrease back down to Step 4 dose.
f. The assessments scheduled for Visit 6 are to be performed for any subject who early terminates from the trial.
g. Subjects who receive the Step 3 dose increase (rechallenge) on Day 13 will be instructed to call the site on Day 14 (day after they again receive the Step 3 dose) to ensure that they can tolerate the rechallenge.
h. Informed consent must be obtained before any trial-related procedures are performed.
i. Assessments will be completed using electronic forms. However, if it is not possible to complete electronic form, then paper forms are permitted.
j. All responses will be relative to the subject's condition at Visit 2/Baseline, prior to the first dose of IMP.
k. Full physical and neurological examinations should be completed at Screening and Visit 6/ET. The physical examination should include weight at all time points and height at the Screening Visit only. Physical and/or neurological examinations can be done at any time point during the trial at the investigator's discretion.
l. At Screening, a triplicate set of 12-lead ECGs is required to assess subject eligibility. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period. At all other noted time points, a single ECG is required. All ECGs should be performed after the subject has been at rest in a supine/semi-recumbent position for approximately 3 minutes.
m. Vital sign measurements include blood pressure, heart rate, and body temperature. Duplicate blood pressure and heart rate measurements will be obtained sitting/supine (after 5 minutes of rest) followed by a single standing measurement (after 2 minutes of rising from sitting/supine position). At each visit, body temperature will be obtained once, at the time of the first blood pressure measurement.
n. The "Baseline/Screening" C-SSRS form will be completed for all subjects at Screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at the Baseline Visit to ensure that the subject continues to qualify for the trial. The "Since Last Visit" C-SSRS form will also be completed at all visits after Baseline.
o. Adverse events (serious and non-serious) and concomitant medications should be recorded from screening through the subject's last visit.
p. Dipstick urinalysis results are not to be recorded on the eCRFs; any clinically significant abnormality should be captured as an adverse event.
q. Prolactin results will be partially blinded.

r. A urine drug screen is required at screening; see the exclusion criteria for exclusions based on the urine drug screen. The urine drug screen can be conducted at any time during the trial at the discretion of the investigator.

s. PK samples will be collected at all clinic visits except Day 1. The date and time of the most recent dose, the dose step, and the time of the blood draw will be recorded. For Visit 3 and 4, PK samples to be collected approximately 2 hours post dose. PK samples should be drawn just after the ECGs at all visits.

t. Blood samples for genotyping are to be collected prior to initiation of dosing.

u. Future biospecimen research sample is optional and is to only be collected if signed consent is obtained from the subject. Sample can be collected any time prior to initiation of dosing.

v. The first dose of IMP (at the Baseline Visit) will be taken in the clinic; subjects will be dispensed IMP to take at home between visits. Subjects will be instructed to bring their IMP to each clinic visit and take their daily dose at the clinic on visit days. Compliance will be assessed through self-reporting by the subject and by tablet count.

17.8. Abbreviations

Abbreviation	Definition
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognition
ADAS-Cog13	Alzheimer's Disease Assessment Scale – Cognition 13-item scale
AE	adverse event
AES-C	Apathy Evaluation Scale-Clinician
AESI	adverse event of special interest
ATC	anatomical therapeutic chemical
CaGI-C	Caregiver Global Impression–Change Scale
CaGI-S	Caregiver Global Impression–Severity Scale
CI	confidence interval
COMT	catechol-o-methyltransferase
COVID-19	coronavirus disease-2019
CRF	case report form
CSP	clinical study protocol
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DAIR	Dementia Apathy Interview and Rating
DCA	diagnostic criteria for apathy
DLB	dementia with Lewy bodies
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ET	early termination
FAS	full analysis set
FTD	frontotemporal dementia
ICF	informed consent form
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intent-to-treat

Abbreviation	Definition
mADCS-CGIC	modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change
mCGI-S	modified Clinical Global Impression–Severity Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
NPI	Neuropsychiatric Inventory
NPI-C	Neuropsychiatric Inventory-Clinician
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TLFs	tables, listings, figures
VAD	vascular dementia
WHO-DD	World Health Organization-Drug Dictionary