CLINICAL PROTOCOL

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

Protocol: CVL-871-2001

Compound Number: CVL-871

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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Regulatory Agency Identifier Number

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IND:	150,086

CONFIDENTIAL – PROPRIETARY INFORMATION

Version 4.0: 14 Feb 2023

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MEDICAL MONITOR NAME AND CONTACT INFORMATION IS PROVIDED IN THE TRIAL OPERATIONS MANUAL

Sponsor Signatories:

PROTOCOL VERSION 4.0 SUMMARY OF CHANGES TABLE

Document History	
Document:	**Date (Day-Month-Year)**
Version 4.0	14 Feb 2023
Version 3.0	08 Apr 2022
Version 2.0	19 Feb 2021
Original Protocol Version 1.0	17 Nov 2020

A summary of the protocol amendment issued prior to the present amendment is provided in Section 10.8.

Amendment: Protocol Version 4.0 (14 Feb 2023)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to modify the number of assessments performed to reduce the burden in an elderly patient population.

Section # and Name	**Description of Change**	**Brief Rationale**
Synopsis Schedule of Assessments 3 Objectives and Endpoints 4.2 Scientific Rationale for Trial Design 8.7 Pharmacodynamic Assessments	Minimize cognitive assessment by removal of Digit Span (WAIS-IV), Trail Making Test (Part A), and COWAT	Reduce burden for elderly patient population
Synopsis Schedule of Assessments 3 Objectives and Endpoints 4.2 Scientific Rationale for Trial Design 8.7 Pharmacodynamic Assessments	Minimize assessments by removal of DAD	Reduce burden for elderly patient population
Synopsis Schedule of Assessments 3 Objectives and Endpoints 4.2 Scientific Rationale for Trial Design 8.7 Pharmacodynamic Assessments 9.4.1 General Considerations	Remove assessment of caregiver burden (assessed using Zarit Burden Interview)	Reduce burden for elderly patient population

Section # and Name	Description of Change	Brief Rationale
Synopsis Trial Schematic 4.1.1 Screening/Baseline Period 9.2 Sample Size Determination	Added flexibility for total number of subjects required for trial	This is an exploratory trial. With the target trial population of patients with dementia-related apathy, a sample size between 60 and 75 should provide sufficient data to assess effect of CVL-871 without undue delay
Synopsis 9.2 Sample Size Determination	In sentence referring to extending enrollment due to higher anticipated early terminations, removed language "due to COVID-19 or other reasons"	Modification due to impacts from COVID pandemic no longer necessary
Trial Schematic Schedule of Assessments 4.1.2 Treatment Period 6.2 Preparation/Handling/ Storage/Accountability/ Disposition	Modified such that Visits 3, 4, and 7 will only be conducted on site	Option for remote visits to accommodate potential issues due to COVID-19 pandemic no longer necessary
Schedule of Assessments 4.1.1 Screening/Baseline Period	Added information that extension of screening period beyond 30 days is permitted in rare cases with medical monitor approval	Additional flexibility needed due to length of screening/baseline visit and need for caregiver to also be present at visits
Schedule of Assessments 4.1.2 Treatment Period	Removed psychosocial intervention	Reduce burden in elderly patient population
Schedule of Assessments 4.1.2 Treatment Period	Removed 4-hour post-dose observation period at Visit 3 and Visit 4	Reduce burden for elderly patient population. Visits 3 and 4 will be conducted in clinic; subjects will be monitored following dosing while concurrently undergoing scheduled assessments
Schedule of Assessments	Added clarification that prolactin results will be "partially" blinded	Procedural clarification
5.1 Inclusion Criteria	Modified such that total body weight has to be greater than or equal to 50 kg (110 lbs)	Mathematical inconsistency as 50 kg is 110.2 lbs
5.2 Exclusion Criteria	Removed sentence regarding exclusion of subjects with symptoms of agitation of aggression that are being controlled using SSRIs/SNRIs from Exclusion #1	Maintain consistency with changes made to prior/concomitant medications permitted

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added to Exclusion #1 that anxiety or depressive symptoms secondary to dementia or other medical condition are not exclusionary provided they are not the primary diagnosis and are stable	Updated to be more reflective of proposed target patient population
5.2 Exclusion Criteria	Modified exclusionary scores on NPI for other NPI subdomains of disinhibition, agitation/aggression, delusions, and hallucinations in Exclusion #4	Update to be more reflective of proposed target patient population
5.4 Screen Failures	Modified to allow for more than 1 rescreening to be conducted with medical monitor approval	Increase flexibility needed for elderly patient population
6.5.2 Prohibited Medications	Reduced period required for stable doses of cholinesterase inhibitors, memantine, and SSRI/SNRIs to 60 days	Update to be more reflective of medication use in proposed target patient population
6.5.2 Prohibited Medications	Removed requirements for dosage and indication (agitation/aggression) for SSRI/SNRI use	Update to be more reflective of medication use in proposed target patient population
6.5.2 Prohibited Medications	Added that pregabalin and gabapentin are prohibited unless being used to treat pain, dose has been stable for at least 60 days prior to randomization, and dosage does not exceed recommended limits per US Package Insert	Update to be more reflective of medication use in proposed target patient population
6.5.2 Prohibited Medications	Added armodafinil to list of prohibited prior and concomitant medications	Update to be more reflective of medication use in proposed target patient population
6.5.2 Prohibited Medications	Added in dose limits for age/sex for nonbenzodiazepine sleep agents	Update to be more reflective of medication use in proposed target patient population
6.5.2 Prohibited Medications	Moved footnote regarding additional information on use of nonbenzodiazepine sleep aids into body of table.	Increase prominence of important information so not inadvertently overlooked
6.5.2 Prohibited Medications	Revised wording regarding prohibited nutritional supplements and herbal preparations to indicate these are restricted due to potential CYP3A4 drug-drug interactions rather than central nervous system effect; remove omega 3 fatty acids	Based on literature that these supplements do not have known central nervous system effect and removal of omega 3 fatty acids as it does not interact with CYP3A4

Section # and Name	Description of Change	Brief Rationale
8.5 Treatment of Overdose	Modified language to clarify when a potential overdose should be considered	Removed redundant language and clarified potential overdose
Section 10.6 Appendix 6: Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A (not exhaustive)	Updated table	Reflect current medication use and updates made per Cerevel standards
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors in original protocol

Abbreviations: COVID-19 = coronavirus disease-2019; COWAT = Controlled Oral Word Association Test; DAD = Disability Assessment for Dementia; NPI = Neuropsychiatric Inventory; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; WAIS-IV = Wechsler Adult Intelligence Scale-IV.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Sponsor Name: Cerevel Therapeutics, LLC

Name of Investigational Medicinal Product: CVL-871

Protocol Title: A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Safety, Tolerability, and Pharmacodynamics of CVL-871 in Subjects With Dementia-Related Apathy

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

IND Number: 150,086

Trial Phase: 2a

Treatment/Indication: Treatment of dementia-related apathy

Rationale: CVL-871 is a dopamine D1/D5 receptor partial agonist that is being evaluated for the treatment of dementia-related apathy. The aim of this trial is to evaluate the safety, tolerability, and pharmacodynamics of CVL-871 in subjects with dementia-related apathy.

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: ○ NPI-C apathy domain score ○ NPI apathy domain score ○ DAIR score ○ 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: ○ mADCS-CGIC scores ○ mCGI-S scores ○ CaGI-S scores ○ 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.

Overall Design:

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week trial 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.

The trial will include a 30-day Screening Period, a 12-week Treatment Period, and a 4-week Safety Follow-up Period. Each subject will participate in the trial for up to approximately 20 weeks.

Disclosure Statement: This is a parallel-group treatment trial with 3 arms that are blinded to the subjects and the investigator.

Number of Subjects:

Approximately 150 subjects will be screened to achieve the target of approximately 75 subjects randomly assigned to treatment (25 per group).

The trial may be considered as complete and be closed out following the randomization of 60 subjects in the event of significantly slower recruitment rate than anticipated to avoid unduly long delay of the final analysis.

Key Entry Criteria:

- Male subjects and female subjects of nonchildbearing potential, ages 50 to 85 years, inclusive

- Meet the International Society for Central Nervous System Clinical Trials and Methodology Apathy Working Group diagnostic criteria for apathy in neurocognitive disorders and have clinically significant apathy defined as Neuropsychiatric Inventory (NPI) apathy domain frequency score of ≥2 and NPI apathy domain severity score of ≥2

- Clinical diagnosis of 1 or more of the following:
  a) Possible or probable Alzheimer's disease dementia according to the 2011 National Institute of Aging – Alzheimer's Association score clinical criteria at the Screening Visit; diagnosis must be stable for at least 6 months
  b) Frontotemporal dementia (FTD; behavioral variant FTD, semantic variant primary progressive aphasia, or nonfluent/agrammatic variant primary progressive aphasia)
  c) Vascular dementia (ie, not vascular cognitive impairment) due to either of the following:
     a. Large vessel or atherothromboembolic disease
     b. Small vessel disease according to the diagnostic criteria for vascular cognitive disorders
  d) Possible or probable dementia with Lewy bodies according to the revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies

Intervention Groups, Trial Treatment, and Duration:

Subjects will be randomized in a 1:1:1 ratio to receive CVL-871 1.0 mg QD, CVL-871 3.0 mg QD, or placebo QD. The dose of CVL-871 will be titrated to the target dose using

a fixed titration scheme. Randomization will be stratified by use of allowed serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor at the time of randomization (as applicable). The planned duration of treatment is 12 weeks. The investigational medicinal products (IMPs) will be taken orally.

Statistical Methods:

Sample Size Estimation: While formal hypothesis testing is not the key objective of this trial, a target 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 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 excluding zero). A minimum sample size of 60 subjects randomized 1:1:1 to the 3 treatment groups would allow this exploratory trial to detect an effect size of 0.761 with 80% power at a 2-sided alpha level of 0.2, and thus would be considered adequate. A discontinuation rate of 20% was taken into consideration in the sample size calculations. 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.

Statistical Methods: Descriptive statistical methods will be used to summarize the data from this trial. Pharmacodynamic endpoints with repeated post-baseline assessments will be analyzed for the modified intent-to-treat (mITT) population using a mixed-model repeated measures (MMRM) analysis, including baseline score (if applicable), treatment, concomitant selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor use, visit, 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.

The trial is designed as a learning trial instead of a confirmatory trial. The key research question for the pharmacodynamic endpoints will be primarily addressed with an estimand based on the following attributes: 1) treatments as randomized regardless of the final dose level achieved following the titration steps, 2) subjects in the mITT population who reach dose increases to at least Step 4 on Day 21 during titration as the target trial population, 3) change from Baseline to Week 12 as the key time point for assessing change from baseline in measured endpoints of interest, 4) the treatment differences estimated based on the least square mean and the corresponding 80% confidence interval from the MMRM model as the population level summary, and 5) a hypothetical strategy to address intercurrent events (ICEs) of potential death, treatment discontinuations, missed visits, and start of prohibited concomitant medications, unless a treatment-related reason can be identified for a given ICE. As the trial is of exploratory nature, a hypothetical strategy will be used to address the ICEs unless a treatment-related reason can be identified for an ICE. If such reasons are identified, a composite strategy may be taken, eg, assigning highest severity to the case, to ensure appropriate interpretation of the data. Further details, including additional estimands for the research questions on the

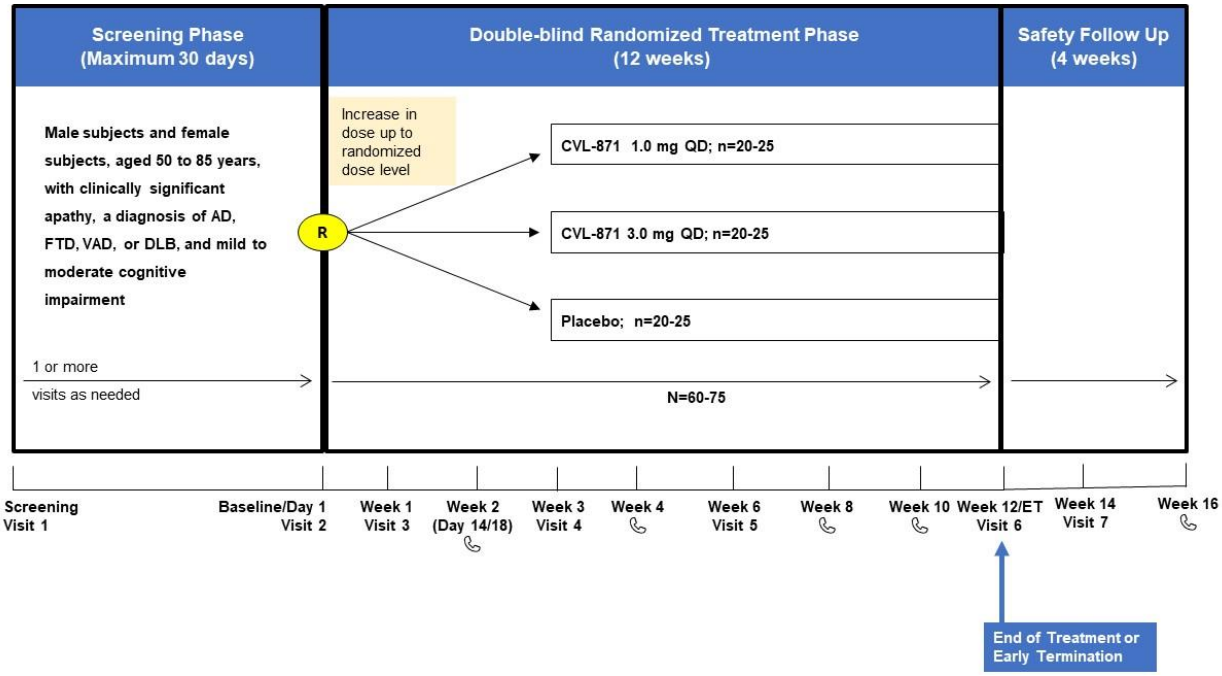
effect of combined CVL-871 treatment group versus placebo and on the effect of final dose levels of CVL-871 following the completion of titration versus placebo, will be described in the statistical analysis plan.

Safety Review Team:

A Safety Review Team will review the blinded safety data from this trial.

1.2 Schema

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.

1.3 Schedule of Assessments

Table 1 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		
NPI-C (dysphoria)		X					X			X		
DAIR		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**						
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]	←----------											----------→
Laboratory												
Blood for safety laboratory sample	X	X	X		X		X			X	X	
Urine for safety laboratory[p]	X	X	X		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**						
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; 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; CaGI-C = Caregiver Global Impression–Change Scale; CaGI-S = Caregiver Global Impression–Severity Scale; 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. See Section 4.1.2.
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. See Section 4.1.2.
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. See Section 8.3.3 for more details.
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.

2 INTRODUCTION

2.1 Trial Rationale

CVL-871 is a dopamine D1/D5 receptor partial agonist that is being evaluated for the treatment of dementia-related apathy that is thought to arise from insufficient dopaminergic signaling. The aim of this trial is to evaluate the safety, tolerability, and pharmacodynamics of CVL-871 in subjects with dementia-related apathy.

2.2 Background

2.2.1 Disease Background

Dementia is a progressive disorder, characterized by a decline in cognition involving multiple domains, that can significantly affect social or occupational function. It is currently estimated that approximately 50 million people worldwide are affected by dementia with numbers increasing by approximately 10 million per year (World Health Organization, 2019). Dementia has a strong negative emotional impact on patients and caregivers, and the economic burden is estimated to be 818 billion dollars per year worldwide (Prince et al, 2015). Several conditions cause dementia; the most common are Alzheimer's disease (AD; ~50% to 70% of cases), frontotemporal dementia (FTD; ~20% of cases), vascular dementia (VAD; ~5% of cases), and dementia with Lewy body (DLB; ~5% of cases; Cunningham et al, 2015).

Although dementia is primarily defined based on cognitive and functional impairment, neuropsychiatric symptoms, such as agitation, delusions, hallucinations, depression, sleep disturbance, and apathy, are common features in most patients.

Apathy in neurocognitive disorders was defined in 2009 by a task force (Robert et al, 2009), and updated by the 2018 International Consensus Group (Robert et al, 2018) as a quantitative reduction of goal-directed activity in comparison with the patient's previous level of functioning. The proposed diagnostic criteria in the 2018 revision required that symptoms be persistent for at least 4 weeks and affect at least 2 of 3 apathy dimensions: 1) behavior/cognition, 2) emotion, and 3) social interaction. More recently, the International Society for CNS Clinical Trials and Methodology (ISCTM) Working Group on Apathy, which included members from the Food and Drug Administration (FDA), has updated the diagnostic criteria for apathy (DCA) of neurocognitive disorders, which is now in prepublication. The updated consensus DCA has refined the 3 core clinical domains to the following: 1) diminished initiative (less spontaneous and/or active than usual self), 2) diminished interest (less enthusiastic about usual activities), and 3) diminished emotional expression/responsiveness. An apathy diagnosis, based on the ISCTM updated DCA, retains the requirement from the 2018 International Consensus Group (Robert et al, 2018) for symptoms to be persistent or frequently recurrent for at least 4 weeks in at least 2 of the 3 core clinical domains (Miller et al, 2021).

Clinically significant apathy is one of the most prevalent and important neuropsychiatric symptoms in patients with dementia (Benoit et al, 2012; Bjoerke-Bertheussen et al, 2012; Cipriani et al, 2014; van der Linde et al, 2012; Breitve et al, 2018). Apathy represents a constellation of symptoms, such as social disengagement, cognitive impairment, and loss of emotion that result in impaired decision-making, loss of interest in personal wellbeing or external issues, inability to initiate and maintain activities, and interference with complex and basic daily function, including motivation to eat, dress, maintain personal hygiene, and take medications (Ishii et al, 2009; Lanctôt et al, 2017; Landes et al, 2001; Nobis and Husain, 2018).

Apathy has been demonstrated to predict functional status in patients with dementia independent of age, global cognition, memory and executive function, and comorbid depression (You et al, 2015; Boyle et al, 2003; Freels et al, 1992). The presence of apathy has been shown to be related to decreased quality of life, increased morbidity and mortality, and early institutionalization and greater resource utilization resulting from increased caregiver distress and burden (Nobis and Husain, 2018; van Dijk et al, 1994; Spalletta et al, 2015; Nijsten et al, 2017; Onyike et al, 2007; Hongisto et al, 2017; Bakker et al, 2013; Landes et al, 2001; George, 2013; Kaufer et al, 1998; Dauphinot et al, 2015). In addition, apathy is a key predictor of progression from mild cognitive impairment to AD dementia (Palmer et al, 2010; Richard et al, 2012; Starkstein et al, 2006). Therefore, the management of apathy is an important component in caring for patients with dementia.

Currently, there are no approved treatments for apathy. Consequently, pharmacologic treatment of patients is comprised of off-label use of drugs such as acetylcholinesterase inhibitors, selective serotonin reuptake inhibitors (SSRIs), and psychostimulants (eg, methylphenidate). Acetylcholinesterase inhibitors, such as donepezil and rivastigmine, have shown only limited effects in clinical trials (Rea et al, 2014; Theleritis et al, 2019; Berman et al, 2012). Use of antidepressants, such as SSRIs, for apathy treatment in dementia is not supported by clinical evidence, and may actually contribute to worsening effect (Barnhart et al, 2004; Wongpakaran et al, 2007; Theleritis et al, 2019; Berman et al, 2012).

2.2.2 Dopaminergic Signaling in Apathy

A pronounced loss of dopamine function in prefrontal cortex occurs along with the natural aging process. Deficient D1 receptor signaling has been directly implicated in age-related declines of cognitive functions including memory capacity and flexibility (Volkow et al, 1998; Bäckman and Farde, 2001). For example, with advancing age, there is a prominent loss of dopamine and dopamine metabolism in the dorsolateral prefrontal cortex and anterior cingulate cortex of monkeys and humans (Ota et al, 2006). Both cognitive deficits and prefrontal cortex dopamine depletion emerge early in the aging process and progressively worsen with advancing age (Bachevalier et al, 1991). Changes in the prefrontal cortex, one of the most sensitive regions to aging influences, usually precede age-related changes in the majority of other cortical regions in individuals without dementia (Raz et al, 2000), and may increase vulnerability to the development of

several neurophysiological disturbances and neuropsychiatric disorders. Positron emission tomography trials demonstrate a loss of striatal D1 but not D2 receptors in patients with AD vs matched controls (Kemppainen et al, 2000).

There is a clear scientific basis for considering the mesolimbic dopamine system as a key part of the neurocircuitry that modulates motivation and reward processing, and thus a potential target for treatment of apathy (Le Heron et al, 2019). Motivated behaviors have been demonstrated to involve the dopaminergic mesolimbic brain reward system (Salamone and Correa, 2012; Ruthirakuhan et al 2018). In addition, apathy has been shown to be associated with neuroimaging changes in specific medial frontal cortex and subcortical structures and these changes are consistent across a disparate range of underlying pathologies (Berridge and Arnsten, 2013; Kos et al, 2016; Le Heron et al, 2018). Agents that can correct imbalances or deficits in the dopaminergic tone within those regions may promote normalization of impaired motivation, reward processing, and goal-directed behaviors (Mitchell et al, 2011).

Evidence supporting the hypothesis that modulation of dopamine signal may improve apathy in patients with dementia has been obtained from clinical trials with methylphenidate (Rosenberg et al, 2013; Padala et al, 2018). Significant improvements in apathy symptoms were reported following treatment with 20 mg/day. Although the exact mechanism involved in methylphenidate's effect on apathy is poorly understood, there is sufficient evidence pointing towards increase of extracellular dopamine levels in striatum and prefrontal cortex by blockade of dopamine transporters (Volkow et al, 2001; Volkow et al, 1998; van Dyck et al, 2020), which are critical regions of the mesolimbic reward system that modulates goal-directed behavior (Le Heron et al, 2018). Following a single oral dose of 60 mg of methylphenidate, dopamine levels in striatum increased, which was evidenced by reduction of raclopride (selective D2 antagonist) by approximately 20% (Volkow et al, 2001).

Dopamine acts on 5 receptor subtypes, which have distinct localization and primary signaling cascades and are commonly divided into 2 groups based on their function. The D1-like family includes the D1 and D5 subtypes, which stimulate cellular activity by increasing intracellular cyclic adenosine monophosphate (cAMP) levels, and the D2-like family includes the D2, D3, and D4 subtypes, which decrease intracellular cAMP when activated. Both D1-like and D2-like family receptors are involved in the dopaminergic pathways of the mesolimbic system that control reward-based decision-making and motivation, with apparent divergent distribution and mechanistic roles, similar to the delineations observed in the nigrostriatal motor circuits (Lopez et al, 2017; Keeler et al, 2014; West and Grace, 2002; Hikida et al, 2010).

Given their distribution, D1 receptors are thought to play important roles in regulating affective, reward-related, and motivational processes, including promotion of goal-directed behavior and learning from positive outcomes (de la Mora et al, 2010; Katz et al, 2006; D'Aquila and Galistu, 2012; Short et al, 2006; Baik, 2013; Wall et al, 2011; Flanigan and LeClair, 2017; Bromberg-Martin et al, 2010; Beninger and Miller, 1998). For example, Yohn and coworkers (Yohn et al, 2015) demonstrated specific impact of D1

agonism as a driver of goal related behavioral activation and increased effort in rodents using an effort-based decision-making task to compare the efficacy of selective D1 agonists reversing the effects of a selective D1/D5 receptor antagonist. In addition, Schweimer (Schweimer and Hauber, 2006) demonstrated that D1, but not D2 receptors, regulate effort-based decision-making in the rodent anterior cingulate cortex, while Soutscheck (Soutschek et al, 2020) showed that a D1 agonist increased the willingness of healthy volunteer subjects to exert effort for reward.

2.2.3 Pharmacological Treatment of Apathy

As described above, there are no currently approved treatments for apathy; however, significant improvements in apathy symptoms in patients with AD were reported following treatment with methylphenidate (Rosenberg et al, 2013; Padala et al, 2018). Despite the observed positive treatment response, adverse effects of methylphenidate-containing medications (eg, anxiety, weight loss, delusions, irritability, hypertension), which would be significant for older persons with a dementing illness, may limit their overall clinical utility for the treatment of dementia-related apathy (Theleritus et al, 2017). A retrospective case-control study of adult methylphenidate users with attention deficit hyperactivity disorder (including more than 4,000 adults ≥65 years of age), showed that initiation of methylphenidate treatment was associated with nearly a doubling of the rate of sudden death or ventricular arrhythmia (propensity score adjusted overall hazard ratio 1.84; in users ≥65 years of age 1.73; Schelleman et al, 2012). These findings are consistent with the current approved labeling for methylphenidate-containing medications in the United States (US), which contain a Warning for Serious Cardiovascular Events in adults, noting "Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD" (Ritalin package insert, 2019; Concerta package insert, 2017).

In addition, psychostimulants like methylphenidate-containing medications have significant abuse potential and are Schedule II controlled substances in the US. Furthermore, broad clinical experience has also established that, in contrast to reuptake inhibition, direct activation of dopamine receptors by selective and nonselective dopamine agonists does not produce immediate euphoria leading to abuse of these agents. Accordingly, none of the currently approved dopamine agonists have been classified as a scheduled drug under the Controlled Substances Act. Furthermore, they have safety profiles that do not show frequent incidences of pleasurable adverse events (eg, euphoria, drunk, high). A search of PubMed revealed no publications that describe the abuse of dopamine agonists, while a search of the Drug Abuse Warning Network database showed that dopamine agonists have not been associated with a significant number of visits to emergency departments for misuse/abuse in the period of 2004 to 2011. From these evidential sources, it can be concluded that the risk for human abuse posed by dopamine agonists is negligible in the generally population.

Therefore, due to the potential risks for abuse, serious cardiovascular side effects, and other systemic and psychological side effects that can be associated with use of psychostimulants, which may be more concerning in an elderly adult population, there remains a need for the evaluation of new dopaminergic therapies for the treatment of

dementia-related apathy that can provide meaningful therapeutic benefit while limiting the risk of significant side effects.

Given the proposed role of D1 receptor activation in regulation of the motivation neurocircuitry, the use of a D1-specific partial agonist for the treatment of dementia-related apathy in elderly patients may be beneficial. While currently available D2/D3 full agonists can be associated with dose-limiting hypotension/acute orthostasis, hallucinations, impulse control disorders, and sudden daytime sleepiness (Stowe et al, 2008; Antonini et al, 2009), these are believed to be mechanistically and specifically linked to D2/D3 receptor activation (Monti and Monti, 2007; Howes and Kapur, 2009; Seeman, 2015; Lopez et al, 2017; Vriend, 2018). Thus, D1 activation with a specific partial agonist is not expected to convey these same risks.

2.2.4 CVL-871

CVL-871 is a dopamine D1 receptor partial agonist being evaluated for the treatment of dementia-related apathy.

In vitro functional testing against recombinant human D1 (hD1) and D5 (hD5) receptors established that the compound is an agonist, which stimulates cAMP formation with the concentration required for half maximal effect (EC_{50}) values of 46 nM and 34 nM, respectively. Comparison of the cAMP response to the full agonist dopamine indicated that CVL-871 is a partial agonist at D1 receptors with intrinsic activity (maximum effect) of 44% and 58% for the hD1 and hD5 receptors, respectively.

CVL-871 has been evaluated for safety and tolerability in 2 clinical trials. In Trial B7821001, the safety, tolerability, and pharmacokinetics (PK) of CVL-871 were evaluated in single ascending dose (SAD) and multiple ascending dose (MAD) cohorts of healthy subjects. Overall, CVL-871 was safe and well tolerated in 48 healthy subjects following single oral doses of up to 1 mg (n=16) and multiple doses of up to 3 mg once daily (QD; n=32). A Phase 1b trial (B7821002) in Parkinson's disease patients (n=19; age range for subjects who received CVL-871 was 54 to 74 years) with motor fluctuations showed that a 3 mg QD dose of CVL-871 (1 mg for Day 1-3 and 3 mg for Days 4-7) resulted in improvement of motor scores, suggesting dopaminergic activity in brain regions involved in motor function (Gurrell et al, 2018). Safety data available from patients treated with CVL-871 (n=10) indicated that CVL-871 was generally safe and well tolerated in this trial. There were no deaths, serious adverse event (SAEs), or severe adverse events (AEs) reported in either trial. The most frequently reported AE in both the SAD and MAD phases of Trial B7821001 and in Trial B7821002 was nausea.

Please refer to the CVL-871 Investigator's Brochure for more detailed information on nonclinical studies and clinical trials.

The aim of this exploratory trial is to evaluate the safety, tolerability, and pharmacodynamics of 2 doses of CVL-871 for treatment of apathy in subjects with dementia-related apathy. In addition, data from this trial will be used to evaluate the appropriateness of currently available apathy clinical assessments in an interventional

setting. Current evidence suggests that CVL-871 has the potential to promote normalization of impaired dopamine signaling at D1 receptors in brain regions that control reward and motivation, while limiting the risk of significant side effects that are associated with psychostimulants and nonselective or D2/3 preferring dopamine agonists.

2.3 Benefit/Risk Assessment

This trial is designed primarily to generate safety, tolerability, and pharmacodynamic data for further clinical development of CVL-871 in a subject population with dementia-related apathy.

As described in Section 2.2.1, dementia-related apathy is a major health problem with no currently approved treatments. Given the proposed role of D1 receptor activation in regulation of the motivation neurocircuitry, the use of a D1-selective partial agonist, such as CVL-871, for the treatment of dementia-related apathy in elderly patients may be beneficial.

Based on the safety and toxicology data available to date, the doses chosen are not expected to pose any significant safety risk to the subjects.

Reproductive and developmental toxicity studies with CVL-871 have not been conducted. In the absence of reproductive or developmental toxicology data, women of childbearing potential are excluded from participation in this trial.

More detailed information about the known and expected benefits and potential risks and expected adverse events of CVL-871 are found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

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: ○ NPI-C apathy domain score ○ NPI apathy domain score ○ DAIR score ○ 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: ○ mADCS-CGIC scores ○ mCGI-S scores ○ CaGI-S scores ○ 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.

4 TRIAL DESIGN

4.1 Overall Design

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week trial to evaluate the safety, tolerability, and pharmacodynamics of 2 fixed doses of CVL-871 (1.0 mg QD and 3.0 mg QD) in male and female subjects aged 50 to 85 years who have dementia-related apathy. The trial will include a 30-day Screening Period, a 12-week Treatment Period, and a 4-week Safety Follow-up Period (Table 1). Each subject will participate in the trial for up to approximately 20 weeks.

4.1.1 Screening/Baseline Period

Subjects who provide written informed consent will be screened for eligibility during the Screening Period. Subjects who are confirmed to be eligible for the trial will be scheduled for a Baseline Visit within 30 days after the Screening Visit 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. Eligible subjects will be randomized in a 1:1:1 ratio to 3 treatment groups at the Baseline Visit:

- CVL-871 1.0 mg QD
- CVL-871 3.0 mg QD
- Placebo QD

Approximately 150 subjects will be screened to achieve the target of approximately 75 subjects randomly assigned to treatment (25 per group). The trial may be considered as complete and be closed out following the randomization of 60 subjects in the event of significantly slower recruitment rate than anticipated to avoid unduly long delay of the final analysis.

Randomization will be stratified by 2 distinct strata: 1) subjects currently using SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) during the trial, 2) subjects not using SSRIs or SNRIs during the trial (see Section 6.5).

4.1.2 Treatment Period

The dose of CVL-871 will be titrated in a blinded fashion to either 1.0 mg QD or 3.0 mg QD and then maintained for the duration of the 12-week Treatment Period, as shown in Table 3. Subjects will be administered a combination of CVL-871/placebo tablets across all doses throughout the trial to maintain the trial blind.

Table 3 CVL-871 and Placebo Dosing Schedule

Trial Day	Titration Step	Target Dose		Placebo QD
		CVL-871 1.0 mg QD	CVL-871 3.0 mg QD	
Days 1-3:	Step 1	0.25 mg CVL-871 QD	0.25 mg CVL-871 QD	Placebo QD
Days 4-7:	Step 2	0.5 mg CVL-871 QD	0.5 mg CVL-871 QD	Placebo QD
Days 8-16:	Step 3	1.0 mg CVL-871 QD	1.0 mg CVL-871 QD	Placebo QD
Days 17-21:	Step 4	1.0 mg CVL-871 QD	2.0 mg CVL-871 QD	Placebo QD
Days 22-84:	Step 5	1.0 mg CVL-871 QD	3.0 mg CVL-871 QD	Placebo QD

Abbreviation: QD = once daily.

This titration scheme will be implemented for all treatment groups, including placebo, in a blinded fashion for all subjects who are randomized. Exceptions for subjects who experience tolerability issue at specific time points are described below.

The first dose of investigational medicinal product (IMP; Step 1) will be taken at the trial site at the Baseline Visit (Day 1). No deviations in the titration schedule up through Step 2 are allowed. Subjects who cannot achieve or tolerate the dose at Step 2 must be discontinued from the trial.

On Day 8 (Visit 3), subjects will take the Step 3 dose of IMP at the clinic. Subjects will be monitored for tolerability while undergoing concurrent assessments; after completion of all visit procedures, the investigator will assess whether the participant will continue with the new dose. Subjects who are unable to tolerate the dose at Step 3 may go back to the dose at Step 2. These subjects will remain at the Step 2 dose until Day 13, at which time they will again receive the Step 3 dose (rechallenge). Subjects 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. Subjects who are unable to tolerate the Step 3 dose upon rechallenge will be discontinued from the trial.

On Day 17, all subjects will take the Step 4 dose; subjects will be contacted by phone on Day 18 and evaluated for tolerability after the dose increase. Subjects who are unable to tolerate the Step 4 dose will be discontinued from the trial.

On Day 22 (Visit 4), all subjects will take the Step 5 dose of IMP at the clinic. Subjects will be monitored for tolerability while undergoing concurrent assessments; after completion of all visit procedures, the investigator will assess whether the participant will continue with the new dose. Subjects who are unable to tolerate the dose at Step 5 may go back to the dose at Step 4 and continue on that dose for the remainder of the trial. Subjects who are able to tolerate the Step 5 dose will continue on this dose for the remainder of the trial and no further dosing adjustments are allowed.

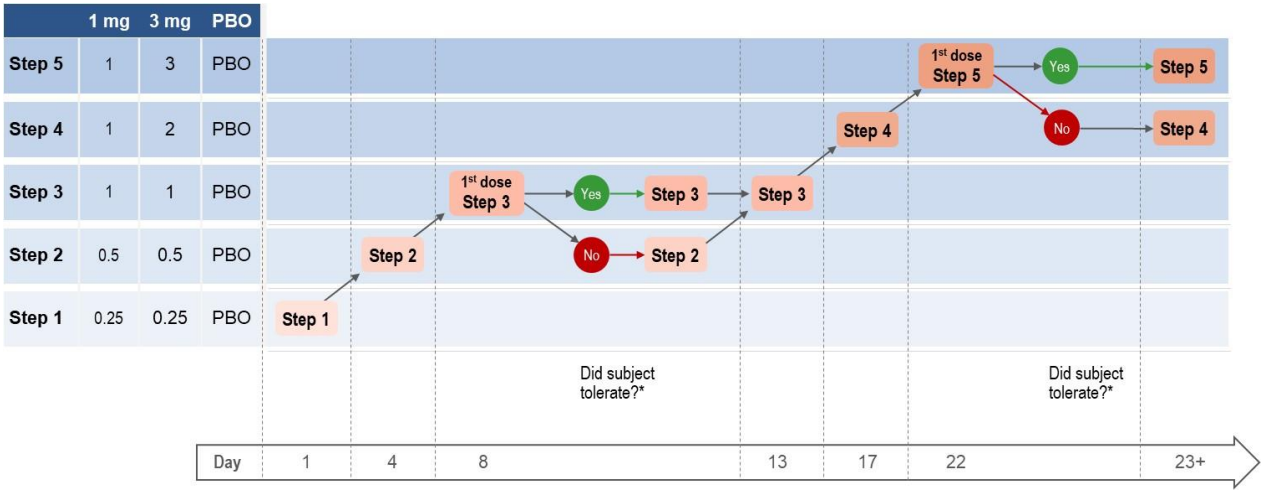
Lack of tolerability should be of sufficient severity that it results in significant dysfunction or distress to the subject (eg, Common Terminology Criteria for Adverse Events [CTCAE] Grade 2/3). The medical monitor should be contacted in any instance

where the investigator is uncertain whether the subject is able to tolerate the stepwise dose increase.

No deviations in the dosing schedule, other than those noted above, are allowed.

The titration scheme, including the dosing decision time points, is presented in Figure 2.

Figure 2 Dosing Schematic



Abbreviations: PBO = placebo.
Note: If "Yes" then continue with new dose; if "No" then stay at previous dose.

Assessments will be conducted at the Week 1, 3, 6, and 12 visits. Subjects will be instructed to take their dose of IMP at the clinic on days when visits occur. Blood samples for PK analysis will be collected at the Week 1, 3, 6, and 12 visits.

4.1.3 Safety Follow-up Period

Subjects will have a Safety Follow-up visit at 14 days after discontinuation of IMP (either after completing the full 12-week Treatment Period or upon premature discontinuation from the trial). Subjects will also be contacted at 4 weeks after the last dose of IMP.

4.1.4 Definition of Completed Subject

A subject is considered to have completed the trial if he/she has completed all phases of the trial including the last Treatment Period visit (Visit 6/Week 12), as shown in the Schedule of Assessments in Section 1.3.

A subject who completed all procedures except the Follow-up visit (Visit 7) and Follow-up phone contact would not be considered an early termination subject.

4.2 Scientific Rationale for Trial Design

The randomized, double-blind, placebo-controlled, parallel-group trial design is widely accepted as one that minimizes the risk of bias and that is appropriate for evaluating the effects of a trial treatment in indications in which use of a placebo is ethical (US FDA, 2001). Randomization reduces bias in the assignment of subjects to a treatment group, the double-blind design prevents differential treatment and assessments, and the placebo-controlled design controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the drug.

The 12-week duration of the current trial should be of sufficient length to show a treatment effect on apathy symptoms. Previous trials examining the effect of methylphenidate on apathy symptoms should a significant effect of methylphenidate compared with placebo at 4 weeks (using Apathy Evaluation Scale-Clinician [AES-C] scale; Padala et al, 2018) and 6 weeks (using Neuropsychiatric Inventory-Clinician [NPI-C] scale; Rosenburg et al, 2013).

To date, there is no accepted standard for evaluation of symptoms of dementia-related apathy in elderly subjects. Therefore, in this trial, apathy and other neuropsychiatric symptoms will be evaluated using several assessments including the apathy domain of the NPI-C, the Neuropsychiatric Inventory (NPI; all 12 domains, including apathy), the Dementia Apathy Interview and Rating (DAIR), and the AES-C. The cognition assessment used is the Alzheimer's Disease Assessment Scale–Cognition (ADAS-Cog) 13-item scale (ADAS-Cog13). Other assessments include the modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (mADCS-CGIC), modified Clinical Global Impression-Severity Scale (CGI-S), Caregiver Global Impression–Severity Scale (CaGI-S), and the Caregiver Global Impression–Change Scale (CaGI-C).

One of the aims of this trial will be to collect data that will be used to evaluate the appropriateness of valid apathy assessments in an interventional setting, which may serve as a primary outcome measure for subsequent trials. The appropriateness would be determined by a scale's ability to correlate with the new diagnostic criteria, reflecting changes in the domains that define the underlying neurobiology, as well as reflecting changes that are meaningful to clinicians, patients, and caregivers.

The safety endpoints, including physical and neurological examinations, vital sign measurements, electrocardiograms (ECGs), laboratory evaluations, and AEs, are those commonly used to assess the safety and tolerability of trial treatments. The Columbia-Suicide Severity Rating Scale (C-SSRS) is commonly used for stringent monitoring of suicidality in clinical trials of neurological compounds (Posner et al, 2011).

4.3 Dosing Rationale

Significant improvements in apathy symptoms have been reported following treatment with methylphenidate in patients with AD (Rosenberg et al, 2013; Padala et al, 2018). As mentioned previously, 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. The top dose of 3 mg QD CVL-871 has been demonstrated to provide improvement of motor symptoms in patients with Parkinson's disease (Gurrell et al, 2018). This dose was well tolerated and was achieved using a quick titration scheme in both healthy subjects and patients with Parkinson's disease. Based on in vitro estimates, this dose is expected to result in approximately 80% occupancy at target receptors in humans. The terminal elimination half-life of 24 hours is expected to provide stable plasma concentrations, approximately 2-fold peak-to-trough ratio, following QD dosing. Based on exposures from B7821001, 3 mg QD is the maximum dose that can be administered without exceeding the exposure limiting criteria based on nonclinical toxicological data.

The lower dose of 1.0 mg QD will provide the pharmacodynamic data at approximately 60% target occupancy. Data from these 2 doses will support evaluation of the dose relatedness of the response. It is important to acknowledge the potential that optimizing cortical D1 circuitry may show significant sensitivity to several factors beyond dose, including individual baseline dopaminergic state, genetics, central nervous system (CNS) disease and neurodegeneration, and concomitant medication that impact dopamine neurotransmission. 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.

In order to mitigate the effects of nausea and vomiting, the target doses of CVL-871 will be achieved using a slow titration paradigm. 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 was successful in achieving the target dose of 3 mg in healthy subjects (B7821001) with minimal tolerability issues. Moreover, for subjects who do experience tolerability issues associated with dose increases at prespecified time points during the trial (see Section 4.1.2), down titration options are available to improve tolerability.

4.4 End of Trial Definition

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

5 TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

General and Administrative	
1.	Male subjects and female subjects of nonchildbearing potential, ages 50 to 85 years, inclusive, at the time of signing the ICF. Women of nonchildbearing potential are defined as follows: • Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause. • Premenopausal women with 1 of the following categories are considered to be of nonchildbearing potential: ○ Documented hysterectomy ○ Documented bilateral salpingectomy ○ Documented bilateral oophorectomy For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determine trial entry. Note: Documentation can come from the site personnel's review of the subject's medical records or medical history interview.
2.	Sexually active men with female partners of childbearing potential must agree to practice acceptable birth control (at minimum), as defined in Section 10.4 (Appendix 4), during the trial and for 4 weeks after the last dose of IMP.
3.	Body mass index of 18.5 to 35.0 kg/m^2 and a total body weight ≥50 kg (110 lbs).
4.	Have a reliable caregiver, defined as an identified adult who is willing to participate in the trial and who spends greater than 10 hours a week with the potential subject, supervises his/her care, and will accompany the subject to trial visits. The caregiver must, in the opinion of the investigator, be able to knowledgeably report on the subject's daily cognition, function, behavior, safety, compliance, and adherence to protocol requirements. The same caregiver must assist the subject throughout the duration of the trial.
5.	Subjects/legally authorized representative and caregiver are capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF.
6.	Ability, in the opinion of the investigator, of the caregiver and subject to understand the nature of the trial, participate in trial visits, and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, outcomes measures, and other trial procedures.
Target Disease Characteristics	
7.	Meet the ISCTM Apathy Working Group diagnostic criteria for apathy in neurocognitive disorders (Miller et al, 2021) at the Screening Visit.
8.	Have clinically significant apathy, defined as NPI apathy domain frequency score of ≥2 and NPI apathy domain severity score of ≥2 at Screening and Baseline Visits.

9.	Have a clinical diagnosis of 1 or more of the following: a) Possible or probable AD dementia according to the 2011 NIA-AA score clinical criteria (McKhann et al, 2011) at the Screening Visit; diagnosis must be stable for at least 6 months prior to signing the ICF[a] b) Frontotemporal dementia of any of the following subtypes: a. Behavioral variant FTD (Rascovsky et al, 2011) b. Semantic variant primary progressive aphasia (Gorno-Tempini et al, 2011) c. Nonfluent/agrammatic variant primary progressive aphasia (Gorno-Tempini et al, 2011) c) VAD (ie, not vascular cognitive impairment) due to either of the following: a. Large vessel or atherothromboembolic disease b. Small vessel disease according to the diagnostic criteria for vascular cognitive disorders (Sachdev et al, 2014) d) Possible or probable DLB according to the revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (McKeith et al, 2017) Note: Subjects who meet the criteria above for more than 1 form of the allowed dementias (eg, mixed dementia) are eligible for the trial.
10.	Have an MMSE score of 12 through 26, inclusive, at the Screening Visit.
11.	Have prior neuroimaging evidence (CT or MRI) collected after the onset of dementia symptoms that is consistent with the diagnosis of AD, FTD, VAD, or DLB and not reflecting any other underlying structural abnormality potentially causing dementia; eg, hydrocephalus, tumor. Note: in the event a subject does not have available neuroimaging evidence but is otherwise eligible for the trial, the medical monitor should be contacted for discussion on eligibility.

Abbreviations: AD = Alzheimer's disease; CT =computed tomography; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; ICF = informed consent form; IMP = investigational medicinal product; ISCTM = International Society for CNS Clinical Trials and Methodology; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NIA-AA = National Institute of Aging – Alzheimer's Association; NPI = Neuropsychiatric Inventory; VAD = vascular dementia.

a Subjects with a definitive diagnosis of Alzheimer's disease based on the 2018 NIA-AA criteria (Jack et al, 2018) are eligible for enrollment.

5.2 Exclusion Criteria

Subjects are excluded from participation in the trial if any of the following criteria apply:

Medical History	
1.	Subjects with a diagnosis of another significant psychiatric disorder per DSM-5 including, but not limited to, anxiety disorders or major depressive disorder (current diagnosis) or schizophrenia or bipolar disorder (current diagnosis or history) at the time of signing the ICF. Subjects with anxiety OR depressive symptoms that are secondary to dementia or another medical condition are not exclusionary provided they do not meet criteria for a primary diagnosis, are relatively stable, and are not expected to change during the trial.

2.	Subjects with a current diagnosis of a neurological disorder other than AD, FTD, VAD, or DLB including, but not limited to, the following: • History of hemorrhagic strokes ascertained by history and/or brain imaging findings • History ischemic stroke or transient ischemic attacks within 12 months prior to signing the ICF • History of multiple ischemic strokes or ischemic stroke with persistent physical disability • History of clinically serious brain infection • History of or current space occupying cerebral lesion or extra-axial lesion producing a mass effect • History of clinically significant concussion or repeated head trauma associated with sustained cognitive impairment in the 5 years prior to signing the ICF • Huntington's disease • Parkinson's disease • Dementia related to substance use disorder • Normal pressure hydrocephalus • Tourette's syndrome • History of seizures (except for childhood febrile) or epilepsy
3.	Subjects with an acute or chronic, clinically significant medical or psychiatric condition or laboratory abnormality that is not otherwise specified in these exclusion criteria that might increase the risk associated with trial participation or administration of trial treatment or interfere with the interpretation of the trial results or that, in the judgment of the investigator, would make the subject inappropriate for entry into this trial. Medical conditions that are minor or well controlled may be considered acceptable if the condition is stable and does not expose the subject to an undue risk of a significant AE or interfere with the assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical conditions(s) and the potential impact of the condition(s) on trial participation.
4.	Subjects with either of the following at the time of the Screening Visit based on any single NPI domain score in agitation/aggression, hallucinations, delusions, or disinhibition: • Frequency score is a 4 (very frequently) OR • Frequency score is a 3 (frequently) AND the severity score is either 2 (moderate) or 3 (severe)
5.	Subjects with a history of impulse control disorder or clinically significant impulsive, socially inappropriate, or compulsive behavior secondary to dementia.
6.	Delirium or history of delirium with the 30 days prior to signing the ICF per investigator judgment or medical history (eg, caretaker reports or medical records).
7.	Subjects with a history of myocardial infarction with residual atrial, nodal, or ventricular arrhythmias that are not controlled with medical and/or surgical intervention; second- or third-degree atrioventricular block; sustained ventricular tachycardia/ventricular fibrillation; sick sinus syndrome; or severe or unstable angina. A recent (≤12 months) history of myocardial infarction with secondary arrhythmias is exclusionary regardless of the therapeutic control.

8.	Subjects with symptomatic heart failure, as defined by the following New York Heart Association functional classes: • Class III – Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. • Class IV – Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms are present even at rest or minimal exertion. If any physical activity is undertaken, discomfort is increased.
9.	Subjects with a history of atrial fibrillation or chronic thrombosis requiring treatment with anticoagulants, eg, warfarin, rivaroxaban (see Table 6).
10.	Subject with a recent history (<6 months) of clinically significant orthostatic hypotension or falls.
11.	Subjects who answer "yes" on the C-SSRS Suicidal Ideation Item 4 or Item 5 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan, or Active Suicidal Ideation with Specific Plan and Intent) and whose most recent episode meeting the criteria for C-SSRS Item 4 or Item 5 occurred within the last 6 months, **OR** Subjects who answer "yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting the criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide.
12.	Subjects with substance abuse or dependence disorder, including alcohol, benzodiazepines, and opioids, but excluding nicotine, within 6 months prior to signing the ICF.
13.	Subjects with any condition or surgery that could possibly affect drug absorption, including, but not limited to complicated appendectomy or cholecystectomy, bowel resections, bariatric weight loss surgery, gastric banding, or gastrectomy.
14.	Subjects with a history of malignancy other than the following: • Non-metastatic basal or squamous cell carcinoma of the skin or carcinoma in situ that was surgically removed in total >1 year before signing the ICF and had not recurred • Another type of malignancy that had been in remission for ≥5 years before signing the ICF and had not recurred • Subjects with history of localized malignancy that was surgically removed and has been in remission for <5 years may be eligible for the trial only with explicit approval by the medical monitor
Prior or Concomitant Medications	
15.	Subjects with a positive urine drug screen or a positive test for alcohol are excluded (note: individuals who test positive for alcohol may be rescreened). Subjects with a positive urine drug screen resulting from use of marijuana (any THC-containing product), prescription, or over-the-counter medications or products that, in the investigator's documented opinion, do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor.
16.	Subjects who are using prohibited medications prior to randomization (as listed in Table 5) or who would be likely to require prohibited concomitant therapy (as listed in Table 6) during the trial.

Physical Examination and Clinical Laboratory Results	
17.	Subject with clinically significant orthostatic hypotension at screening associated with either of the following: • Loss of consciousness (eg, syncope) • Presyncope (eg, severe dizziness/lightheadedness) requiring stabilization to avoid fall
18.	• Subjects with a supine/sitting blood pressure ≥160 mmHg (systolic) or ≥100 mmHg (diastolic). The average of 2 supine/sitting measurements will be used to assess eligibility. • For subjects with a supine/sitting blood pressure ≥140 mmHg (systolic) or ≥90 mmHg (diastolic), approval is required by medical monitor on a case-by-case basis. • Subjects receiving >2 antihypertensive medications for blood pressure control.
19.	Subjects with a 12-lead ECG demonstrating a QTcF interval ≥450 msec. At Screening (Visit 1): • Subjects with an ECG QTcF interval ≥450 msec based on the average of a centrally read triplicate set of ECGs. At Baseline (Visit 2): • If the QTcF interval is ≥450 msec on the machine reading, consult the medical monitor to determine whether the subject remains eligible to be randomized while awaiting the reading from the central service.
20.	Subjects with moderate to severe renal impairment (defined as Stage 3b estimated glomerular filtration rate <45 mL/min/1.73 m^2, as calculated using the 4 parameters Modification of Diet in Renal Disease formula [Levey et al, 1999]).
21.	Subjects with any of the following abnormalities in clinical laboratory tests at the Screening Visit, as assessed by the central laboratory and confirmed by a single repeat measurement, if deemed: • AST or ALT ≥2 × ULN • Total bilirubin ≥1.5 mg/dL. Subjects with a history of Gilbert's syndrome may be eligible provided they have a value <ULN for direct bilirubin • Positive result for HIV antibodies, HbsAg, or HCV antibodies ○ If a subject has completed treatment for hepatitis and is in remission with a viral load of 0, they may be eligible for the trial only with explicit approval by the medical monitor
22.	Subjects with uncontrolled thyroid disease or clinical laboratory results indicating hypo- or hyperthyroidism at the time of signing the ICF.
23.	Subjects with other abnormal laboratory test results, vital sign results, or ECG findings unless, in the judgment of the investigator, the findings are not medically significant and would not impact the safety of the subjects or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria provided in the protocol.
Other	
24.	Subjects who previously participated in any CVL-871 trial, including this trial, and received IMP.

25.	Subjects who received treatment with any other investigational drug within 60 days before signing the ICF or who have participated in more than 2 drug intervention clinical trials within the year prior to signing the ICF.
26.	Subjects who have a known or suspected intolerance or hypersensitivity to the IMP, closely related compounds, or any of their stated ingredients.
27.	Subjects with significant communicative, auditory or visual impairment that would affect their ability to do neuropsychological testing or take part in a clinical trial, based on investigator judgment.
28.	Subject who resides in a long-term continuous care facility.
29.	Subject who is non-ambulatory or wheelchair bound.
30.	Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.

Abbreviations: AD = Alzheimer's disease; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; DLB = dementia with Lewy bodies; ECG = electrocardiogram; FTD = frontotemporal dementia; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IMP = investigational medicinal product; NPI = Neuropsychiatric Inventory; QTcF = QT interval corrected for heart rate using Fridericia's formula; THC = tetrahydrocannabinol; ULN = upper limit of normal range; VAD = vascular dementia.

5.3 Lifestyle Considerations

Subjects should take the IMP at approximately the same time each day (preferably in the morning at ~24-hour intervals), with or without food. No lifestyle restrictions are imposed.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) at screening may be rescreened at the discretion of the investigator and after consultation with the medical monitor, unless screen failure is due to a positive urine drug screen. Rescreened subjects will be assigned a new subject number.

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial subject according to the trial protocol. Investigational medicinal product refers to a pharmaceutical form of

any active substance or placebo being tested in this clinical trial and will be used to refer to the trial treatment in this protocol.

6.1 Trial Treatments Administered

A summary of the IMP administered during this trial is presented in Table 4.

Table 4 Investigational Medicinal Product Administered

Treatment Group	CVL-871	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Matching tablet
Unit Dose Strengths	0.25, 0.5, 1, 2, and 3 mg	0 mg
Dosage Levels	1 and 3 mg QD	0 mg
Route of Administration	Oral	Oral
Sourcing	Provided centrally by Cerevel	Provided centrally by Cerevel
Packaging and Labeling	Trial treatment will be provided in bottles. Each dispensable unit will be labeled as per country requirement.	Trial treatment will be provided in bottles. Each dispensable unit will be labeled as per country requirement.

Abbreviations: QD = once daily.

6.2 Preparation/Handling/Storage/Accountability/Disposition

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit (original shipment and/or moving of IMP supply from 1 office or facility to another within the sites network) for all IMP received and any discrepancies are reported and resolved before use of the IMP. In cases where caregivers/subjects are taking IMP from the site to their home following a site visit, it is not required for caregivers/subjects to document IMP temperature conditions during transit.

Only subjects enrolled in the trial or their caregivers may be dispensed IMP and only authorized site staff or designee may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the preparation, handling, storage, accountability, and disposition of IMP are provided in the pharmacy manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Subject Assignment to Treatment

During the entire trial, treatment will be double-blind, ie, neither the investigator nor the subject will have knowledge of the treatment assignment at any visit.

Treatment assignments will be based on a computer-generated randomization code provided by Cerevel or designee. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment codes during the trial. 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 SAEs to regulatory agencies.

Once a randomization number has been assigned, it must not be reassigned.

6.3.2 Blinding

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 (as shown in Table 3) to be made without breaking the trial blind.

Treatment assignments will be blinded to the investigators and other trial site personnel, the subjects, and all sponsor personnel who are involved in the conduct of the trial (including trial monitoring, data management, and data analysis). Access to the treatment codes will be restricted to personnel who are responsible for generating and maintaining the randomization code, packaging the IMPs, operating the IRT, analyzing the PK blood samples, or reporting SAEs or adverse events of special interest (AESI) to regulatory agencies.

Although the integrity of blinding is critical to the validity of the trial assessments, subject safety must always be the first consideration. The IRT will be programmed with blind-breaking instructions. At the initiation of the trial, investigators and site personnel will be instructed on the method for breaking the blind in the event of subject safety emergency. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment assignment is warranted. However, the investigator should make every effort to contact the medical monitor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the medical monitor must be notified within 24 hours after breaking the 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.

6.4 Trial Treatment Compliance

Responsible trial personnel will dispense the IMP. The time and dose of each IMP administration, along with information on any missed or inappropriately administered dose, will be recorded in source documents and the electronic case report form (eCRF).

The guidance and intent of this trial is for caregivers to administer IMP. Therefore, subjects and caregivers must be counseled on the importance of taking the IMP as directed. If poor compliance is encountered (eg, multiple missed doses resulting in less than 80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. Subjects who habitually miss visits or habitually attend visits outside of the protocol-defined visit window are also defined as noncompliant and should be considered for discontinuation. The medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

6.5 Prior and Concomitant Therapy

6.5.1 Prior and Concomitant Medications

The investigator will record all medications and therapies (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on the eCRF. The investigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in the eCRF: therapy, indication, start date, and end date.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.2 Prohibited Medications

All subjects must agree to discontinue all prohibited medications per times defined in Table 5. Other medications to treat medical conditions that are not specifically defined below are allowed.

Table 5 Prohibited Prior Medications

	Prohibited Prior Medications	Prohibited Duration of Use Prior to Randomization
1.	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)
2.	Antipsychotics	3 months
3.	Tricyclic antidepressants and bupropion	30 days
4.	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)
5.	Trazodone >50 mg/day for the treatment of depression.	30 days
6.	Mood stabilizers and anticonvulsants (eg, lithium, valproate, carbamazepine)	30 days
7.	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)
8.	Benzodiazepines	30 days
9.	Opioid analgesics	30 days
10.	• 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
11.	Atomoxetine, modafinil, armodafinil, and varenicline	30 days
12.	Psychostimulants (eg, methylphenidate, amphetamine, lisdexamfetamine)	30 days
13.	Levodopa and/or other dopamine agonists (including levodopa inhalation powder or apomorphine)	7 days[a]

	Prohibited Prior Medications	Prohibited Duration of Use Prior to Randomization
14.	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	30 days
15.	Strong or moderate inducers or inhibitors of CYP3A4 metabolism (see Section 10.6 [Appendix 6]).	Inhibitors: 5 half-lives or 30 days (shorter of the 2) Inducers: 5 half-lives or 21 days (longer of the 2)
16.	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.
a. Contact the medical monitor for additional instruction if needed.

Table 6 lists all medications prohibited during the trial, including exceptions where appropriate. Initiation of a new medication for treatment of a medical condition may be permitted if it is medically indicated due to a change in the subject's underlying medical condition and is not otherwise prohibited (eg, cytochrome P450 [CYP] interaction). Consultation with the medical monitor is encouraged.

Table 6 Prohibited Concomitant Medications

	Prohibited Concomitant Medications
1.	Cholinesterase inhibitors and memantine are prohibited with the following exception: o 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 o SSRI and SNRI antidepressants are allowed provided the following: ▪ 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 o Nonbenzodiazepine sleep agents (ie, zolpidem, zaleplon, zopiclone, and eszopiclone) and low-dose trazodone (up to 50 mg) are allowed for treatment of insomnia ▪ 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). o 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

	Prohibited Concomitant Medications
11.	Psychostimulants (eg, methylphenidate, amphetamine, lisdexamfetamine)
12.	• Antihistamines with sedating effects (eg, diphenhydramine) o 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). o Anti-platelet medications (eg, aspirin, clopidogrel) are permitted.
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 Section 10.6 [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.

6.6 Dose Modification

This is a fixed-dose trial of CVL-871 1.0 mg QD and CVL-871 3.0 mg QD. The dose of CVL-871 will be titrated to the randomized dose, as shown in Table 3, and then maintained for the remainder of the trial. Procedures for dose modification are provided in Section 4.1.2.

Dose modifications will be achieved by issuing the subject new bottles with the adjusted dose such that the subject continues to take 1 tablet each day. The IMP will be packaged in a manner that will allow dose modifications to be made without unblinding the trial.

6.7 Intervention after the End of the Trial

There will be no provision of CVL-871 for subjects after they complete or discontinue treatment in this trial. Subjects/caregivers should consult with the investigator to determine appropriate treatment regimens following completion or discontinuation of trial treatment.

7 DISCONTINUATION OF TRIAL TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Trial Treatment

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a

disallowed medication or therapy, or other issues, as determined by the investigator. If IMP is permanently discontinued, the subject will be encouraged to remain in the trial for the evaluations at safety follow-up. See the Schedule of Assessments (Table 1) for data to be collected at the time of discontinuation of IMP and follow-up and for any further evaluations that need to be completed.

The IMP may be discontinued for any of the following reasons listed below:

- Adverse event
- Protocol deviation
- Noncompliance with study schedule
- Withdrawal by subject
- Physician decision

If a subject discontinues the IMP due to an AE, the investigator or other trial personnel will make every effort to follow the event until it has resolved or stabilized.

7.2 Discontinuation of Trial

7.2.1 Discontinuation of Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and regulatory authorities in accordance with regulatory requirements.

7.2.2 Discontinuation of Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

7.2.3 Individual Subject Discontinuation From the Trial

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary.

At the time of discontinuing from the trial, if possible, an early termination visit should be conducted, as shown in the Schedule of Assessments (Table 1). See the Schedule of Assessments (Table 1) for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

The subject will be permanently discontinued both from the IMP and from the trial at that time.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.3 Procedures to Encourage Continued Trial Participation

In all cases of impending consent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) with the subject their options of continuing in the trial. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.4 Lost to Follow up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site personnel.

The following actions must be taken if a subject fails to return to the site for a required trial visit:

- The site personnel must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial.

8 TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the Schedule of Assessments (Table 1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue trial intervention.

Adherence to the trial design requirements, including those specified in the Schedule of Assessments, is essential and required for trial conduct.

8.1 Screening and Baseline Assessments

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Protocol waivers or exemptions are not allowed. The investigator will maintain a screening log to record details of all subjects who are screened and to confirm eligibility or record reasons for screening failure, as applicable.

The sponsor reserves the right to utilize oversight methods to ensure the validity of diagnosis, severity of illness, and other factors determining appropriateness of subject selection.

Procedures that are conducted as part of the subject's routine clinical management (eg, blood count) and obtained before the informed consent form (ICF) is signed may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame that is defined in the Schedule of Assessments (Table 1).

The following screening tests will be completed to ensure the subject is suitable for inclusion in the trial.

8.1.1 Diagnostic Criteria for Apathy

The subject will be evaluated for apathy at screening using the recently published ISCTM diagnostic criteria for apathy in neurocognitive disorders (see Section 5.1; Miller et al, 2021). These criteria require that a subject's must meet all 4 of the following: 1) meet criteria for a syndrome of cognitive impairment or dementia, 2) exhibit at least 1 symptom in 2 of 3 domains (diminished initiative, diminished interest, diminished emotional expression/responsiveness), which are persistent or frequently recurrent for a minimum of 4 weeks and represent a change from patient's normal behavior, 3) symptoms are not exclusively explained by other factors, and 4) symptoms cause clinically significant impairment in personal, social, occupational, and/or other important areas of functioning.

8.1.2 Mini Mental State Examination

The Mini Mental State Examination (Folstein et al, 1975) will be conducted at screening to evaluate the subject's mental status and confirm it meets the inclusion criteria score of 12 to 26 (see Section 5.1).

8.1.3 Neuropsychiatric Inventory Rating Scale

The NPI (see Section 8.7.1) will be utilized at screening for confirmation of subject's clinically significant apathy (see Section 5.1) and to rule out exclusionary comorbid psychiatric diagnoses (see Section 5.2).

8.2 Efficacy Assessments

Not applicable; pharmacodynamic assessments are discussed in Section 8.7.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Table 1).

Safety assessments should be performed after all pharmacodynamic assessments have been completed. Assessments should be performed in the following order:

- C-SSRS
- Physical and neurological examinations
- Vital sign measurements
- ECGs

- Blood specimen collection
- Other procedures (eg, concomitant medications, AEs): all other procedures may be obtained before or after blood specimen collection

8.3.1 Physical Examinations

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.

The following guidelines will aid in the standardization of body weight measurements:

- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments)

The investigator (or designee) is responsible for performing the physical and neurological examinations. If the appointed designee is to perform these examinations, he or she must be permitted by local regulations and his or her name must be included on the delegation of authority log. Whenever possible, the same individual should perform all physical and neurological examinations.

Any condition present at the post-treatment physical and neurological examinations that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

8.3.2 Vital Sign Measurements

Vital signs 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 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.

Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF.

Further details on taking vital sign measurements are provided in the appropriate trial specific manuals.

8.3.3 Electrocardiograms

Electrocardiogram recordings will be obtained after the subject has been supine/semi-recumbent and at rest for approximately 3 minutes. Additional ECGs may be obtained at the investigator's discretion and should always be obtained in the event of early termination. The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. 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.

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. If, during screening, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject or the interpretation of the trial results) or meets an exclusion criterion (see Section 5.2), the subject should be excluded from the trial. 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 specified time points in the Schedule of Assessments (Table 1) where an ECG recording must be performed, only a single ECG is required. If, at the Baseline Visit, the QTcF interval is ≥450 msec on the machine reading, consult the medical monitor to determine whether the subject remains eligible to be randomized while awaiting the reading from the central service.

Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. A repeat ECG should be performed to confirm any clinically significant abnormality that is identified in a randomized subject during the treatment period (which will be confirmed by central service read) and, in these cases, the medical monitor should be consulted on the appropriateness of the subject continuing in the trial.

8.3.4 Clinical Safety Laboratory Assessments

See Section 10.1 (Appendix 2) for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Table 1) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the medical monitor notified.

All protocol-required laboratory assessments, as defined in Section 10.1 (Appendix 2), must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Table 1).

8.3.5 Suicidal Ideation and Behavior Risk Monitoring

Suicidality will be monitored during the trial using the C-SSRS. This semi-structured interview was originally developed to evaluate the link between antidepressants and suicidal behavior and ideation in youth and adverse events from pediatric clinical trials (Posner et al, 2011). It was designed to quantify the severity of suicidal ideation and behavior. Trial personnel administering the C-SSRS must have completed the appropriate training and have valid certification. Access to training on the scale will be provided by the sponsor or designee.

This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. Any subject with active suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (Section 5.2).

The "Since Last Visit" C-SSRS form will be completed at all visits after screening. The investigator will review the results of the "Since Last Visit" C-SSRS during the trial to determine whether it is safe for the subject to continue in the trial. If a subject demonstrates potential suicidal ideation associated with actual intent or method or plan as indicated by "YES" answers on item 4 or 5 of the C-SSRS, the investigator will evaluate whether a risk assessment by a qualified mental health professional (or the investigator alone if the investigator is a qualified mental health professional) is needed and whether the subject should continue in or be discontinued from the trial.

8.4 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or trial procedures, or that caused the subject to discontinue IMP (see Section 7)

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until follow-up contact on Day 113 at the time points specified in the Schedule of Assessments (Table 1).

All SAEs will be recorded and reported to the medical monitor immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the medical monitor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the trial, and he/she considers the event to be reasonably related to the IMP or trial participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.4.4 Regulatory Reporting Requirements for SAEs/AESIs

Prompt notification by the investigator to the Sponsor regarding an SAE/AESI is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review, acknowledge, and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

Details of all pregnancies in female partners of male subjects will be collected after the start of IMP and until the final contact on Day 113.

If a pregnancy in a female partner is reported, the investigator should inform the medical monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Adverse Events of Special Interest

All AESIs should be reported according to the procedures and timelines for SAEs (see Section 10.3.4).

Brief narratives will be written for any subject who reports an AESI.

8.4.6.1 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

8.4.6.2 Nausea Grade 3

- Grade 3 nausea, defined as inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition, or hospitalization indicated

8.4.6.3 Vomiting Grade 2 or Higher

- Grade 2 vomiting, defined as vomiting requiring outpatient intravenous hydration or other medical intervention (eg, anti-emetic)

8.4.6.4 Abnormal Liver Function Tests

The finding of an elevated value for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of >3 × the upper limit of normal (ULN) in combination with either an elevated value for total bilirubin >2 × ULN or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Investigators must report the occurrence of either of the following as AESI to the sponsor with 24 hours:

- Treatment-emergent value of >3 × ULN for ALT or AST and >2 × ULN for total bilirubin
- Treatment-emergent value of >3 × ULN for ALT or AST and clinical jaundice

8.4.6.5 Abnormal Dreams/Nightmares

Either of the following AEs:

- Abnormal dreams
- Nightmares

8.4.6.6 Adverse Events Potentially Related to Abuse

A key objective of the Abuse Potential Monitoring Plan (APMP) is to monitor for instances of abuse or diversion of the trial medication and other psychoactive substances.

In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue will also receive special attention. As part of the APMP, medication handling irregularities (MHIs) must be reported, and AEs related to abuse potential and AEs involving MHIs must be reported as events subject to additional monitoring (ESAMs), with detailed narratives.

Investigators and site staff at each trial site will be trained on reporting potentially abuse-related AEs (eg, recording a description of the event in the subject's own words in the source documents as well as the eCRF, in addition to the clinical term, and to be aware that a subject's report may encompass more than one event and that these should

be recorded separately). The investigators will be provided with examples of potentially abuse-related AEs and trained on how to handle such events (eg, additional monitoring).

While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search by the sponsor of all relevant Medical Dictionary for Regulatory Activities (MedDRA) terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, consistent with US FDA guidance (Guidance for Industry: Assessment of Abuse Potential of Drugs, January 2017).

Complete details, including documenting and reporting procedures, examples of potentially abuse-related terms and guidance for the training of investigators and trial site staff are provided in the APMP.

8.4.6.7 Adverse Events Leading to Discontinuation

Any AE that leads to discontinuation of IMP or from the trial will be classified as an AESI.

8.5 Treatment of Overdose

For this trial, any dose of CVL-871 greater than 3 mg/day could potentially be considered an overdose. Refer to Table 3 for the number of tablets that could result in the maximum dose at each titration step. Consult with the medical monitor if there are any questions.

There is no specific antidote for overdose with CVL-871. Treatment of overdose should consist of general supportive measures.

In the event of an overdose, the investigator should complete the following:

1. Contact the medical monitor immediately.

2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until CVL-871 can no longer be detected systemically (at least 5 days).

3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of CVL-871, if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

8.6 Pharmacokinetics

Single blood samples will be collected in appropriately labeled tubes for determination of the concentration of CVL-871 in plasma at times specified in the Schedule of Assessments (Table 1).

As part of understanding the PK of CVL-871, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

Additional details regarding the collection, processing, storage, and shipping of all PK plasma samples will be provided in a laboratory manual. All plasma samples will be analyzed for analyte using a validated bioanalytical method.

8.7 Pharmacodynamic Assessments

The planned time points for pharmacodynamic assessments are shown in the Schedule of Assessments (Table 1). At each clinic visit, pharmacodynamic assessments should be completed first, followed by the safety assessments.

A caregiver must be identified during the Screening Period for participation in and/or completion of appropriate assessments.

The same caregiver must assist the subject and complete all assessments throughout the duration of the trial.

8.7.1 Neuropsychiatric Inventory-Clinician 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; 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.

8.7.2 Dementia Apathy Interview and Rating

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 the 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). Items are counted only if the behavior represents a changed 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.

8.7.3 Apathy Evaluation Scale-Clinician

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).

8.7.4 Alzheimer's Disease Assessment Scale – Cognition Subscale

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.

8.7.5 Modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change

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.

8.7.6 Modified Clinical Global Impression-Severity Scale

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".

8.7.7 Caregiver Global Impression-Severity Scale

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".

8.7.8 Caregiver Global Impression-Change Scale

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".

8.8 Pharmacogenomics

Blood samples will be collected for analysis of catechol-O-methyltransferase (COMT) genotype.

8.9 Biomarkers

Biomarkers are not evaluated in this trial.

8.10 Future Biospecimen Research

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them at Cerevel makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, pharmacodynamics, tolerability, or safety not anticipated prior to the beginning of this trial.

Future biospecimen research samples will be collected from subjects who provide additional consent specifically for this sample collection. Research performed on these samples may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects.

8.11 Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The trial is designed primarily to assess the safety and tolerability of CVL-871 in subjects with dementia-related apathy and to estimate the treatment response in pharmacodynamic endpoints. Formal hypothesis testing is not the key objective of this trial of exploratory nature.

9.2 Sample Size Determination

While formal hypothesis testing is not the key objective of this trial, a 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 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 excluding zero). A sample size of 60 subjects randomized 1:1:1 to the 3 treatment groups would allow this exploratory trial to detect an effect size of 0.761 with 80% power at a 2-sided alpha level of 0.2. A discontinuation rate of 20% was taken into considerationin the sample size calculation. 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) .

In the event of higher than anticipated early terminations, Cerevel may extend enrollment in order to maintain the planned statistical power of the trial.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 7 Populations for Analysis

Population	Description
Enrolled	Comprises all subjects who consent to participate in the clinical trial.
Intent-to-Treat	Comprises all randomized subjects.
Full Analysis Set	Comprises all randomized subjects who receive at least 1 dose of IMP.
Modified ITT Set	Comprises all randomized subjects who receive at least 1 dose of IMP and have at least 1 post-baseline assessment of the NPI apathy subscale score.

Abbreviations: IMP = investigational medicinal product; ITT = intent-to-treat; NPI = Neuropsychiatric Inventory.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the details on subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the key statistical analyses planned for the primary and secondary endpoints.

9.4.1 General Considerations

Descriptive statistical methods will be used to summarize the safety/tolerability, pharmacodynamic, and PK data from this trial. Statistical modelling will also be performed for the pharmacodynamic endpoints.

All statistical analyses will be conducted with the SAS® System, version 9.4 or higher. Full details of all planned analyses will be provided in the SAP.

9.4.2 Pharmacodynamic Analyses

Pharmacodynamic endpoints with repeated post-baseline assessments will be analyzed using a mixed-model repeated measures (MMRM) analysis, including baseline score (if applicable), treatment, concomitant SSRI/SNRI use, visit, 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.

The trial is designed as a learning trial instead of a confirmatory trial. The key research question for the pharmacodynamic endpoints will be primarily addressed with an estimand based on the following attributes: 1) treatments as randomized regardless of the final dose level achieved following the titration steps, 2) subjects in the modified intent-to-treat (mITT) population who tolerate dose increases to at least Step 4 on Day 21 during titration as the target trial population, 3) change from Baseline to Week 12 as the key endpoint of interest, 4) the treatment differences estimated based on the least square mean and the corresponding 80% confidence interval from the MMRM model as the population level summary, and 5) a hypothetical strategy to address intercurrent events (ICEs) of potential death, treatment discontinuations, missed visits, and start of prohibited concomitant medications unless a treatment-related reason can be identified for a given ICE. If such reasons are identified, a composite strategy may be taken, eg, assigning highest severity to the case, to ensure appropriate interpretation of the data. Further details, including additional estimands for the research questions on the effect of combined CVL-871 treatment group versus placebo and on the effect of final dose levels of CVL-871 following the completion of titration versus placebo, will be described in the SAP.

9.4.3 Pharmacokinetic Analyses

Plasma concentration data of CVL-871 will be summarized for each dose at each time point using descriptive statistics and graphs.

9.4.4 Safety Analyses

The safety analysis will be conducted on the full analysis set. Analyses will be performed based on the actual treatment received. Treatment-emergent adverse events will be coded according to the MedDRA and summarized by treatment group, system organ class, and preferred term. Further summaries will be done by seriousness, severity, relationship to IMP, and dose at the time of onset.

Other safety endpoints will be summarized with descriptive statistics by treatment group, including suicidality monitored during the trial using C-SSRS.

All data collected for subjects in the screen failures data set will be listed separately.

9.4.5 Interim Analyses

No interim analyses are planned.

9.4.6 Safety Review Team

In addition to routine safety monitoring during trial conduct, a Safety Review Team (SRT) will review blinded safety data at specified time points and provide a recommendation on trial conduct, which will be described in a separate SRT charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical trials (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the subject and caregiver and answer all questions regarding the trial.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (as applicable by local law) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 requirements, where applicable, and the IRB/IEC or trial center. Caregivers will also be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 requirements, where applicable, and the IRB/IEC or trial center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects/legally authorized representatives and caregivers must be reconsented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the subject/legally authorized representative and caregiver.

A separate and similar consent process will be followed for the optional future biospecimen research samples. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data Protection

Subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject and outlined in the ICF.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Trial Data

Cerevel fulfills its commitment to publicly disclose clinical trial results through posting trial results on ClinicalTrials.gov, the European Clinical Trials Database, and other public registries in accordance with applicable local laws/regulations.

In all cases, trial results are reported by Cerevel in an objective, accurate, balanced, and complete manner and are reported regardless of trial outcome or the country in which the trial was conducted.

Clinical trial US Basic Results are posted on Clinicaltrials.gov for all Cerevel-sponsored interventional trials conducted in subjects that evaluate the safety and/or efficacy of a Cerevel product, regardless of the geographical location in which the trial is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.4 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

Cerevel posts European Union (EU) Basic Results on EudraCT for all Cerevel-sponsored interventional trials that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.4 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

10.1.6 Data Quality Assurance

All subject data relating to the trial will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for the longest of the following periods:

- At least 2 years after the date on which approval to market the drug is obtained (or if IMP developments is discontinued, the date regulatory authorities were notified of discontinuation)
- At least 3 years after the sponsor notified the investigator that the final reports has been filed with regulatory authorities
- A longer period if required by local regulations or institutional policies

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

10.1.8 Trial and Site Closure

The sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further trial treatment development

10.1.9 Publication Policy

The results of this trial may be published or presented at scientific meetings at the Sponsor's discretion.

The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 8 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Serology (screening for human immunodeficiency virus, hepatitis B virus, hepatitis C virus) will be done at screening and SARS-CoV2 tests may be done at investigator discretion.

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit Mean corpuscular volume	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood urea nitrogen Creatinine Albumin Cholesterol (total, HDL-C, LDL-C) Triglycerides	Potassium Sodium Calcium Bicarbonate Chloride Magnesium Glucose	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Gammaglutamyl transferase CPK Total bilirubin and direct bilirubin Total protein
Routine Urinalysis	Specific gravity Color pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick[a] Microscopic examination (if blood or protein is abnormal)		
Additional Required Protocol-specific Tests	Prolactin (results will not be reported to investigative sites or other blinded personnel until the trial is unblinded). If serum CPK value is >3 × ULN, CPK reflex for isoenzymes. If serum CPK value is >5 × ULN, serum and urine myoglobin.		
Other Screening Tests	Urine drug screen Test for alcohol Thyroid function testing: thyroid-stimulating hormone, free and total T3, free and total T4 Serology (human immunodeficiency virus antibody, hepatitis B virus, hepatitis C virus), SARS-CoV2 testing (may be done at investigator discretion)		

Abbreviations: AE = adverse event, CPK = creatine phosphokinase; eCRF = electronic case report form; HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SARS-CoV2 = severe acute respiratory syndrome coronavirus 2; T3 = triiodothyronine, T4 = thyroxine; ULN = upper limit of normal range.

a. Results of the dipstick urine analysis will not be recorded on the eCRFs. Any clinically significant finding will be captured as an AE.

Investigators must document their review of each laboratory safety report and file appropriately.

Laboratory results that could unblind the trial will not be reported to investigative sites or other blinded personnel until the trial has been unblinded.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

Table 9 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical trial subject, temporally associated with the use of trial treatment, whether or not considered related to the trial treatment. • NOTE: Signs and symptoms and/or abnormal laboratory test result indicating a common underlying pathology/diagnosis should be reported as a single adverse event.

Table 10 Events Meeting the AE Definition

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after trial treatment administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical manifestations of a suspected drug-drug interaction. • Signs, symptoms, or the clinical manifestations of a suspected overdose of either trial treatment or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

Table 11 Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose in the view of either the investigator or sponsor, results in any of the following outcomes:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

Table 12 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
• The investigator will then record all relevant AE/SAE information in the eCRF.
  ○ Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status noted. All nonserious events (that are not considered AESIs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).
  ○ If updated information (eg, resolved status) on SAE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor according to the appropriate reporting procedures.
  ○ The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.
  ○ Any new SAEs reported to the investigator that occur after the last scheduled contact and are determined by the investigator to be related to the use of the IMP, should be reported to the sponsor. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.
• It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the AE/SAE eCRF page.
• There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

Assessment of Intensity

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v5.0; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)

Adverse events not listed by the NCI-CTCAE will be graded according to the criteria defined below.

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the subject.

Note: An instrumental activity of daily living refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- The investigator will assess the relationship as either of the following:
  - **Related**: An AE will be considered "related" to the use of the IMP if there is evidence to suggest a reasonable possibility of a causal relationship between the IMP and the AE.
  - **Not Related**: An AE will be considered "not related" to the use of the IMP if there is no plausible causal relationship between the IMP and the AE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Table 13 Follow-Up of AEs and SAEs

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs and AESIs

Table 14 SAE Reporting to the Sponsor of Designee via an Electronic Data Collection Tool

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE or AESI to the sponsor or designee will be the electronic data collection tool. • The site will enter the SAE/AESI data as soon as it becomes available within 24 hours of awareness. • If the electronic data collection tool is unavailable, then the site will use the paper SAE or AESI form (see next section). • After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a trial subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on the paper SAE form (see next section) or to the sponsor or designee by telephone.

Table 15 SAE Reporting to the Sponsor or Designee via Paper Form (if needed)

SAE Reporting to the Sponsor or Designee via Paper Form
• If the electronic data collection tool is unavailable, then the site will use the paper SAE/AESI form. The SAE or AESI paper form should be used to electronically transmit this information to the sponsor or designee. • Contacts for electronic transmission of the paper SAE/AESI form are provided in the Operations Manual. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE or AESI data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the appropriate SAE or AESI form within the designated reporting time frames.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

10.4.1.1 Highly Effective Form of Contraception (Failure Rate <1%)

A highly effective form of contraception (failure rate of <1%) is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

10.4.1.2 Acceptable Birth Control Methods (Failure Rate >1% per Year)

Acceptable birth control methods that result in a failure rate of more than 1% per year include the following:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide*
- Cap, diaphragm or sponge with spermicide*

*A combination of male condom with a cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered acceptable but is not a highly effective birth control method.

10.4.1.3 Contraception and Pregnancy Avoidance Procedures

The following definitions apply for contraception and pregnancy avoidance procedures:

A woman is considered a woman of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Sterilized male subjects should be at least 1 year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

10.4.2 Collection of Pregnancy Information

10.4.2.1 Male Subjects With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this trial. This applies only to male subjects who receive IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate

form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Future Biospecimen Research

Use/Analysis of DNA

- Genetic variation may impact a subject's response to IMP, susceptibility to, and severity and progression of disease. Variable response to IMP may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.

- DNA samples will be used for research related to CVL-871, Alzheimer's disease and other dementia disorders, or apathy or other cognition disorders. They may also be used to develop tests/assays including diagnostic tests related to CVL-871 or interventions of this drug class and dementia disorders. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- There are no planned analyses of DNA samples. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

- The samples may be analyzed as part of a multi-trial assessment of genetic factors involved in the response to CVL-871 or IMPs of this class to understand trial disease or related conditions.

- The results of genetic analyses may be reported in the CSR or in a separate trial summary.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained while research on CVL-871 or interventions of this drug class or dementia disorders continues but no longer than 15 years or other period as per local requirements.

10.6 Appendix 6: Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A (not exhaustive)

Note that this is not a complete list and that the investigator is responsible for ensuring that subjects are not receiving any strong or moderate inducers or inhibitors of CYP3A during the trial.

CYP 3A Inhibitors	CYP 3A Inducers
Antivirals	**Antivirals**
Nirmatrelvir/ritonavir[a]	Efavirenz
Indinavir	Nevirapine
Nelfinavir	Etravirine
Ritonavir	Tipranavir
Saquinavir	**Miscellaneous**
Boceprevir	Barbiturates
Lopinavir/ritonavir	Carbamazepine
Amprenavir	Cenobamate
Atazanavir	Eslicarbazepine
Telaprevir	Glucocorticoids (systemic)
Darunavir/ritonavir	Modafinil
Fosamprenavir	Oxcarbazepine[d]
Antibiotics	Phenobarbital
Clarithromycin	Phenytoin
Erythromycin	Rifabutin
Telithromycin	Rifampin
Ciprofloxacin	St. John's wort
Anti-infectives	Bosentan
Itraconazole	
Ketoconazole	
Fluconazole	
Posaconazole	
Voriconazole	
Anti-anginal therapy	
Diltiazem	
Verapamil	
Anti-cancer therapy	
Crizotinib	
Imatinib	
Miscellaneous	
Nefazodone	
Aprepitant	
Grapefruit juice[b]	
Conivaptan	

a Paxlovid (nirmatrelvir co-packed with ritonavir) is prohibited.

b A 2-week washout prior to dosing is required if grapefruit juice was being consumed continually.

10.7 Appendix 7: 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
ALT	alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AST	aspartate aminotransferase
cAMP	cyclic adenosine monophosphate
CNS	central nervous system
COMT	catechol-O-methyltransferase
COVID-19	coronavirus disease-2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAIR	Dementia Apathy Interview and Rating
DCA	diagnostic criteria for apathy
DLB	dementia with Lewy bodies
DNA	deoxyribonucleic acid
DX	dopamine X receptor (1 through 5)
EC_{50}	concentration required for half maximal effect
ECG	electrocardiogram
eCRF	electronic case report form
ESAM	event subject to additional monitoring
EU	European Union
FDA	Food and Drug Administration
FTD	frontotemporal dementia
GCP	Good Clinical Practice
hDX	human DX receptor (D1-D5)
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
ISCTM	International Society for CNS Clinical Trials and Methodology
MAD	multiple ascending dose
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
MedDRA	Medical Dictionary for Regulatory Activities
MHI	medication handling irregularity
mITT	modified intent-to-treat
MMRM	mixed-model repeated measures
NPI	Neuropsychiatric Inventory
NPI-C	Neuropsychiatric Inventory-Clinician
PK	pharmacokinetic
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SNRI	serotonin-norepinephrine reuptake inhibitor
SRT	Safety Review Team
SSRI	selective serotonin reuptake inhibitor
ULN	upper limit of normal
US	United States
VAD	vascular dementia

10.8 Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Document History	
Document:	**Date (Day-Month-Year)**
Version 4.0	14 Feb 2023
Version 3.0	08 Apr 2022
Version 2.0	19 Feb 2021
Original Protocol Version 1.0	17 Nov 2020

Amendment: Protocol Version 3.0 (08 Apr 2022)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to update the inclusion and exclusion criteria to more accurately represent the proposed patient population.

Section # and Name	**Description of Change**	**Brief Rationale**
Signature Page	Updated sponsor signatory	Change in internal responsibilities
Synopsis 4.1.1 Screening/Baseline Period	Increased number of screened subjects from approximately 100 to approximately 150	Adjusted for higher than anticipated rate of screen failures
Synopsis 1.3 Schedule of Assessments 5.1 Inclusion Criteria 8.1.3 Clinical Dementia Rating	Removed the requirement for Global Clinical Dementia Rating score 0.5 to 2.0 for subject to be eligible for trial	Updated to be more reflective of proposed target population and streamline evaluation of dementia
1.3 Schedule of Assessments	Adjusted table such that the "±3 days" window starts at Remote Visit 3 rather than at Visit 2/Baseline	Correction to prior version of protocol
1.3 Schedule of Assessments 4.1.2 Treatment Period	Deleted "up to" text in footnote "v" and other sections referring to observation time following dosing	Correction to prior version of protocol
2.2.1 Disease Background 5.1 Inclusion Criteria 8.1.1 Diagnostic Criteria for Apathy 11 References	Added reference for updated criteria for diagnosing apathy	Reference was not published at time of prior protocol

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	Removed information about risk assessment completed for COVID-19 pandemic effects on trial	Text should not be included in this section of protocol, mitigation efforts will be described elsewhere
5.1 Inclusion Criteria 8.1.2 Mini Mental State Examination	Modified the lower range of MMSE score for inclusion in trial to 12	Updated to be more reflective of proposed target population
5.2 Exclusion Criteria	Removed the caveat allowing subjects with symptoms of anxiety or depression that are stable and adequately controlled to be enrolled	Consistency with change in Exclusion Criterion #4
5.2 Exclusion Criteria	Removed the exclusion of subjects with score >3 on NPI domains for anxiety, irritability, or dysphoria in Exclusion Criterion #4	Updated to be more reflective of proposed target population
5.2 Exclusion Criteria	Modified wording regarding exclusion subjects with conditions that could affect drug absorption	Updated for consistency with Cerevel standards
5.2 Exclusion Criteria 1.3 Schedule of Assessments 5.4 Screen Failures 10.2 Appendix 2: Clinical Laboratory Tests	Modified wording regarding exclusion subjects based on urine drug screen or positive alcohol test	Updated for consistency with Cerevel standards
6.3.2 Blinding	Removed text indicating information regarding documentation of unblinding is in eCRF	Inaccurate as only limited information on unblinding in eCRF (time blind is broken and name of personnel involved only in medical record)
6.5.2 Prohibited Medications	Added levodopa and/or other dopamine agonists to list of prohibited prior and concomitant medications	To rectify oversight of not including these prohibited medications in the previous version of protocol
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors in original protocol

Abbreviations: COVID-19 = coronavirus disease-2019; eCRF = electronic case report form; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory.

Amendment: Protocol Version 2.0 (19 Feb 2021)

This version of the protocol (Version 2.0) represents the first version to be submitted to any health authority; therefore, no subjects were enrolled under Version 1.0.

Overall Rationale for the Amendment:

The overall rationale for the amendment is correct errors in original protocol and ensure the protocol is accurate prior to enrollment of any subjects in the trial.

Section # and Name	Description of Change	Brief Rationale
Synopsis 3 Objectives and Endpoints	Condense safety endpoints and specify defined as "clinically significant changes/findings"	Ensure consistency with Cerevel standard practice
Synopsis 5.1 Inclusion Criteria	Explicitly state in Inclusion Criterion 9 that subjects with more than 1 form of allowed dementias (eg, mixed dementia) may be included in the trial	Modify wording to clarify that subjects with dementia due to more than 1 neurodegenerative cause (eg, mixed dementia) are allowed to participate in the trial
Synopsis 5.1 Inclusion Criteria 11 References	Text and references describing frontotemporal dementia were clarified; reworded to clearly reflect the dementia and subtypes that are allowed	Clarify that subjects with a diagnosis of frontotemporal dementia that is any 1 of the 3 variants are eligible to participate in the trial
Synopsis 5.1 Inclusion Criteria	Expand the accepted inclusion range for Global CDR score and include caveats regarding scores for functional CDR domains	Allow for enrollment of more eligible subjects with mild dementia. The caveat requiring scores >0 in 1 of 3 functional domains ensures the 0.5 Global CDR score indicates early/mild dementia vs mild cognitive impairment/questionable dementia, which is consistent with the 2011 NIA-AA criteria for all-cause dementia.
1.3 Schedule of Assessments	Add information describing which forms are provided in electronic format and which are in paper format and provide clarification that if it is not possible to complete the form in electronic format then it is permissible to do on a paper format	Additional clarification for site personnel
1.3 Schedule of Assessments 5.2 Exclusion Criteria 8.1.3 Clinical Dementia Rating	Remove language requiring a score of ≥2 on the NACC-FTLD Behavior Domain (Item 9) of the CDR Plus NACC FTLD Staging Instrument and replace with language specific to impulse control-related behaviors due to frontotemporal dementia	Original criteria could have resulted in excluding subjects with frontotemporal dementia with significant apathy, loss of empathy or social interest, without other significant impulsive, inappropriate, or compulsive behavior issues.
1.3 Schedule of Assessments 8.7.9 Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change	Add completion of the mADCS-CGIC worksheet at baseline	Inadvertent omission of the baseline version for the mADCS-CGIC to be completed prior to dosing for the rater to use as a reference when completing the post-baseline form

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Assessments	Removed the urine drug screen at Visits 2 and 6/ET	The urine drug screen is only needed at the Screening Visit, unless the investigator feels it is needed during the trial (as described in footnote p)
1.3 Schedule of Assessments	Add line and footnote to indicate site personnel need to request IMP assignment and IMP shipping prior to remote visits	Additional clarification for site personnel
2.2.4 CVL-871	Added age range of subjects to description of Trail B781002	Demonstrate CVL-871 has been tested in an older population
4.1 Overall Design	Move information that was previously included in Section 4.4 Definition of Completed Subject into Section 4.1 as a new subsection (Section 4.1.4)	Ensure consistency with Cerevel standard practice
4.1.1 Screening/Baseline Period	Modify wording regarding randomization stratification by use of SSRIs or SNRIs during the trial	Additional clarification regarding definition of 2 strata
4.1.2 Treatment Period	Add sentence indicating medical monitor should be contacted if investigator needs further clarification on whether subject is able to tolerate the stepwise dose increase	Include process in cases where investigator is unclear as to what defines a lack of tolerability to stepwise dose increase
5.1 Inclusion Criteria	Change timing requirement for subject to need neuroimaging evidence consistent with dementia diagnosis from “within 12 months prior to randomization” to “anytime after onset of dementia symptoms”	Requirement for neuroimaging evidence within 12 months of randomization was deemed too restrictive and not necessary to rule out other causes of dementia. This change is consistent with criteria used in other clinical trials using a clinical diagnosis of dementia.
5.2 Exclusion Criteria	Add text clarifying that space occupying cerebral lesions is inclusive of extra-axial lesions producing a mass effect	Inadvertent omission from protocol; extra-axial lesions producing a mass effect are considered equivocal to space occupying cerebral lesions
5.2 Exclusion Criteria	Separate out anxiety, irritability, and dysphoria scores and increase the exclusionary criteria to scores greater than 3 at Screening or Baseline visits	Prior criteria were too rigid as these symptoms do not represent a confounder to outcomes if present at a level that is not clinically significant (generally defined as NPI domain score of 4 or greater)

Section # and Name	Description of Change	Brief Rationale
6.5.2 Prohibited Medications	Modify footnote a regarding nonbenzodiazepine sleep aids with respect to the maximum allowable daily dose permitted for treatment of insomnia	The dose cap will be enforced to mitigate increase in potential fall risk from higher doses of nonbenzodiazepine sleep aids
8.1 Screening and Baseline Assessments	Add sentence indicating sponsor can employ additional methods to ensure appropriateness of subject selection	Provide flexibility to use additional methods to ensure subjects adequately fulfill entry criteria
8.7.1 Neuropsychiatric Inventory-Clinician and Neuropsychiatric Inventory Rating Scales	Remove text stating the NPI-C screening strategy examines and scores only behavioral domains with positive responses to screening questions	Text removed as it was applicable to situation when NPI-C was administered in its entirety. When only a few domains are administered, the guidance recommends that all items should be administered regardless of the response to the screening questions.
8.7.5 Digit Span: Wechsler Adult Intelligence Scale IV	Modify the digit span length range for forward and backward span	Error in original protocol
8.7.10 Modified Clinical Global Impression-Severity Scale	Update to reflect final text in actual scale	Text for newly created scale was not final in original protocol
8.7.11 Caregiver Global Impression-Severity Scale	Update to reflect final text in actual scale	Text for newly created scale was not final in original protocol
8.7.12 Caregiver Global Impression-Change Scale	Update to reflect final text in actual scale	Text for newly created scale was not final in original protocol
10.5 Appendix 5: Future Biospecimen Research	Add that samples may also be used for research related to apathy or other cognitive disorders	Provide flexibility in case want to investigate findings in data and as they would apply to cognition and apathy more broadly than in just dementia disorders
10.6 Appendix 6: Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A (not exhaustive)[a]	Revise section title and add sentence stating list provided in appendix may not be exhaustive and that the investigator is ultimately responsible for ensuring subjects do not receive any prohibited concomitant medication	List in appendix was not exhaustive and subject to change as new drugs may come to market during the trial period
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors in original protocol

Abbreviations: CDR = Clinical Dementia Rating; ET = early termination; IMP = investigational medicinal product; mADCS-CGIC = modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; NACC-FTLD = National Alzheimer's Coordinating Center-Frontotemporal Lobar Degeneration;

NIA-AA = National Institute of Aging – Alzheimer's Association; NPI-C = Neuropsychiatric Inventory-Clinician; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

a Section number refers to current version of the protocol.

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CLINICAL PROTOCOL PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

Protocol Number: CVL-871-2001

Compound: CVL-871

Trial Phase: 2a

Sponsor Name: Cerevel Therapeutics, LLC

Legal Registered Address: 222 Jacobs Street, Suite 200, Cambridge, MA 02141 United States

Version 4.0: 14 Feb 2023

I, the undersigned principal investigator, have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

Principal Investigator Printed Name

Principal Investigator Signature

Date (DD MMM YYYY)