CLINICAL STUDY PROTOCOL

A Master Protocol for Three, Independent, Seamlessly Enrolling, Double-blind, Placebo-controlled, Efficacy and Safety Studies of ACP-204 in Adults With Alzheimer's Disease Psychosis

Protocol Number: ACP-204-006

Amendment 3

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Title: A Master Protocol for Three, Independent, Seamlessly Enrolling, Double-blind, Placebo-controlled, Efficacy and Safety Studies of ACP-204 in Adults With Alzheimer's Disease Psychosis

Senior Vice President, Head of Clinical Development:
Sanjeev Pathak, MD
Acadia Pharmaceuticals Inc.
502 Carnegie Center, Suite 300
Princeton, NJ 08540 USA
sanjeev.pathak@acadia-pharm.com
Phone: (609) 250-6257

See appended electronic signature page

Signature Date

Acadia Study Lead:
Bryan Dirks, MD
Vice President, Clinical Development
Acadia Pharmaceuticals Inc.
502 Carnegie Center, Suite 300
Princeton, NJ 08540 USA
bdirks@acadia-pharm.com
Phone: (609) 250-6924

See appended electronic signature page

Signature Date

Acadia Biostatistics:
Peter Zhang, PhD
Executive Director, Head of Biostatistics
Acadia Pharmaceuticals Inc.
502 Carnegie Center, Suite 300
Princeton, NJ 08540 USA
peter.zhang@acadia-pharm.com
Phone: (609) 250-6900

See appended electronic signature page

Signature Date

DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the principles of Good Clinical Practice, as required by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6 and as described in the applicable United States (US) Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56, 312, unless prohibited by other applicable local laws and regulations.

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The confidential information in this document is provided to you as an Investigator or Consultant for review by you, your staff, and the applicable institutional review board/ethics committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

Investigator

Signature	Date
Name (printed)	

PROTOCOL SYNOPSIS

Protocol number	ACP-204-006
EU CT number **IND number**	2023-507325-42-00 164067
Protocol title	A Master Protocol for Three, Independent, Seamlessly Enrolling, Double-blind, Placebo-controlled, Efficacy and Safety Studies of ACP-204 in Adults With Alzheimer's Disease Psychosis
Name of investigational product	ACP-204 (capsules)
Indication	Treatment of hallucinations and delusions associated with Alzheimer's disease psychosis (ADP)
Phase of development	2/3
Sponsor	Acadia Pharmaceuticals Inc. 12830 El Camino Real, Suite 400 San Diego, CA 92130 USA
Study hypothesis	ACP-204 will be superior to placebo in the treatment of hallucinations and delusions associated with ADP
Primary efficacy objectives **Part 1** To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared with placebo in subjects with ADP as measured by the Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales (SAPS-H+D) total score **Part 2A and Part 2B** To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared with placebo in subjects with ADP as measured by SAPS-H+D total score.	**Primary efficacy endpoint (Parts 1, 2A and 2B)** Change from Baseline in the SAPS-H+D total score at Week 6
Key secondary efficacy objectives **Part 1** To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared with placebo in subjects with ADP as measured	**Key secondary efficacy endpoint (Parts 1, 2A, and 2B)** CGI-I-ADP score at Week 6

by Clinical Global Impression–Improvement in the ADP context (CGI-I-ADP) **Part 2A and Part 2B** To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared with placebo in subjects with ADP as measured by CGI-I-ADP	
Other secondary efficacy objectives **Part 1** To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared to placebo in subjects with ADP in the following domains: • symptoms of hallucinations and delusions • sleep disturbance **Part 2A and Part 2B** To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared to placebo in subjects with ADP in the following domains: • symptoms of hallucinations and delusions • sleep disturbance	**Other secondary efficacy endpoints (Parts 1, 2A, and 2B)** CGI-I-ADP score at Weeks 1, 2, and 4 Change from Baseline on: • SAPS-H+D total score at Weeks 1, 2, and 4 • Sleep Disorders Inventory (SDI) score at Week 6 Proportion of subjects with: • SAPS-H+D total score ≥30% reduction from Baseline, at all visits • SAPS-H+D total score ≥50% reduction from Baseline, at all visits • SAPS-H+D total score 100% reduction from Baseline or score of 0, at all visits • CGI-I-ADP score of 1 (very much improved) or 2 (much improved), at all visits
Exploratory efficacy objectives **Part 1** To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared to placebo in subjects with ADP in the following domains: • symptoms of hallucinations and delusions • neuropsychiatric symptoms • caregiver distress • occupational disruptiveness • quality of life **Part 2A and Part 2B** To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared to placebo in subjects with ADP in the following domains:	**Exploratory efficacy endpoints (Parts 1, 2A, and 2B)** Change from Baseline on: • SAPS Hallucinations domain (SAPS-H) score at all visits • SAPS Delusions domain (SAPS-D) score at all visits • Clinical Global Impression–Severity in the ADP context (CGI-S-ADP) score at all visits • Neuropsychiatric Inventory (NPI) domain and total scores for subjects with an unpaid caregiver such as family or friend OR Neuropsychiatric Inventory–Nursing Home Version (NPI-NH) domain and total scores for subjects with a paid caregiver at Weeks 2, 4, and 6

• symptoms of hallucinations and delusions • neuropsychiatric symptoms • caregiver distress • occupational disruptiveness • quality of life	• NPI Caregiver Distress total score for an unpaid caregiver such as family or friend OR NPI-NH Occupational Disruptiveness total score for a paid caregiver at Weeks 2, 4, and 6 • NPI Psychosis score at Weeks 2, 4, and 6 • NPI-C Hallucinations domain, Delusions domain, and Psychosis scores at Weeks 2, 4, and 6 • Quality of Life in Alzheimer's Disease (QOL-AD) score at Week 6
Safety objectives **Part 1** To evaluate the safety and tolerability of ACP-204 60 mg and ACP-204 30 mg compared to placebo in subjects with ADP **Part 2A and Part 2B** To evaluate the safety and tolerability of either ACP-204 60 mg or ACP-204 30 mg compared to placebo in subjects with ADP	**Safety endpoints (Parts 1, 2A, and 2B)** • Treatment-emergent adverse events (TEAEs) • 12-lead electrocardiograms (ECGs) • Vital signs, including orthostasis assessment • Weight and body mass index (BMI) • Physical examination results • Clinical laboratory tests • Global Clinician Assessment of Suicidality (GCAS) score • Columbia–Suicide Severity Rating Scale (C-SSRS) • Udvalg for kliniske undersøgelser (UKU) Sleepiness/Sedation and Orthostatic Dizziness scores • Mini-Mental State Examination (MMSE) score • Digit Symbol Substitution Test (DSST) score • Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A) scores

Pharmacokinetic and pharmacokinetic/ pharmacodynamic objectives • To characterize the pharmacokinetics (PK) of ACP-204 in subjects with ADP • To assess the pharmacokinetic/ pharmacodynamic (PK/PD) relationship of ACP-204 using efficacy and safety endpoints in subjects with ADP	**Pharmacokinetic and pharmacokinetic/ pharmacodynamic endpoints** • ACP-204 PK parameters using a population PK approach • PK/PD of ACP-204 using appropriate PK/PD analysis methods
Number of study sites	Approximately 140 global sites for Part 1 and 140 global sites for Part 2A or Part 2B will participate in this study.
Number of subjects planned in Part 1, Part 2A, and Part 2B	A screen failure rate of approximately 60% is expected. In Part 1 (Phase 2) approximately 318 subjects will be randomized in a 1:1:1 ratio to ACP-204 60 mg, ACP-204 30 mg, or placebo treatment. Approximately 106 subjects will be included in each blinded treatment group: ACP-204 60 mg, ACP-204 30 mg, and placebo. Part 2A and Part 2B (Phase 3) will enroll different subjects than Part 1 (Phase 2). It is planned to randomize approximately 378 subjects in each of Part 2A and Part 2B in a 1:1:1 ratio with approximately 126 subjects per treatment group (ACP-204 60 mg, ACP-204 30 mg, and placebo).
Investigational product, dose, and administration	ACP-204 will be provided as 60 mg or 30 mg capsules or matching placebo to be taken orally once daily.
Study design Part 1, Part 2A, and Part 2B	ACP-204-006 is a master protocol for three independent, seamlessly enrolling, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2/3 studies in subjects with ADP. Subjects will be enrolled into either Part 1 (Phase 2), which will evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared with placebo in subjects with ADP, or Part 2A or Part 2B (Phase 3), which will be confirmatory of either both doses or only a single dose from Part 1. Subjects may be enrolled into only one part of the study. No subject may be enrolled into more than one of Part 1, Part 2A, and Part 2B. Sites will begin work seamlessly on either Part 2A or Part 2B when their enrollment in Part 1 is complete. Acadia will alert each site when they can begin enrollment into Part 2A or Part 2B. Sites will be assigned in approximately equal numbers to work on either Part 2A or Part 2B, but not both. The randomization in Part 2A and Part 2B are independent, and their data are managed in two independent and separate databases. This should ensure that Part 2A and Part 2B are truly independent of each other. Subjects who complete Part 1 or Part 2A or Part 2B (i.e., did not

	have an early termination [ET] from the study) will have the option of participating in the long-term open-label extension (OLE) study, ACP-204-008, pending confirmation of eligibility. For subjects who roll over into the OLE study (ACP-204-008), at their end of treatment (EOT) visit, subject consent/assent and study partner/caregiver consent for ACP-204-008 must be provided per local regulations prior to the procedures being performed at the EOT visit, as the EOT procedures for Study ACP-204-006 will serve as the baseline procedures for Study ACP-204-008. Each part of the study will have the following periods, which will be applicable for individual subjects depending on whether the subject rolls over into the OLE and whether they complete the study: • Screening Period (up to 49 days) • Double-blind Treatment Period (6 weeks) • Safety Follow-up Period (30 days) for Subjects Not Rolling Over into OLE (including ET subjects) • Mortality Follow-up for ET Subjects These periods are detailed below and diagrammed in Figure S–1 and Figure S-2. The schedule of assessments is provided in Table S–1. **Screening Period (up to 49 Days)** During the Screening Period, if the subject has a historical positive biomarker in blood or cerebrospinal fluid, or positron emission tomography (PET) imaging, indicating amyloid plaque deposition and neuropathologic change consistent with Alzheimer's disease, then all screening procedures (including those scheduled for Visit 1a and Visit 1b) may be conducted on the same day. If the subject does not have such historical evidence of Alzheimer's disease, then blood biomarker (BBM) positivity is required for eligibility, and Screening will be conducted across at least two visits (Visit 1a and Visit 1b). At Visit 1a, the subject will be consented and have samples collected for all laboratory tests and BBM testing to confirm Alzheimer's disease. The laboratory and BBM test results from Visit 1a will determine whether the subject can progress to Visit 1b of Screening. If there are exclusionary laboratory test results or if the BBM result is negative, the subject will be a screen failure. If the laboratory test results are not exclusionary and the BBM result is positive, the subject and caregiver will return to the clinic to complete Screening (Visit 1b). There may be circumstances in which Visit 1b will need to be performed prior to receipt of results from BBM testing. In such instances, the Investigator should consult the Medical Monitor prior to proceeding with Visit 1b.

	Adult subjects aged 55 to 95 years, inclusive, will be assessed for study eligibility and prohibited medications will be discontinued if medically appropriate. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications should be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician. During the Screening Period, the designated study partner/caregiver will be given instructions on engaging in a structured psychosocial interaction with the subject (brief psychosocial therapy). Subjects who fail Screening may be rescreened for study eligibility with Medical Monitor agreement. **Double-Blind Treatment Period (6 Weeks)** The Baseline visit (Visit 2) may occur up to 49 days after the first Screening visit (Visit 1a). At Visit 2, following confirmation of eligibility, subjects will be randomized in a 1:1:1 ratio to 60 mg ACP-204, 30 mg ACP-204, or matching placebo, and stratified by site and by whether subjects are living in the wider community (not in an institution) or institution living (such as a nursing home). Subjects will then take their first dose of study drug in the clinic and will be dispensed study drug to take home. It is recommended that thereafter the subject take the study drug at approximately the same time each day. Assessments will be conducted at Weeks 0 (Baseline), 1, 2, 4, and 6 (EOT/ET). **Safety Follow-up Period (30 Days) for Subjects Not Rolling Over into OLE** Subjects who successfully complete the 6-week Double-blind Treatment Period may be eligible to enroll in an OLE study (ACP-204-008). For subjects who discontinue prematurely from the study, two Safety Follow-up visits (telephone calls to the subject and study partner/caregiver) should be conducted, at 7 (±3) days and 30 (+4) days after the last dose of study drug, provided the subject or the subject's legally acceptable representative (LAR) has not withdrawn consent from further data collection. **Mortality Follow-up for ET Subjects** In addition to the safety follow-up telephone calls during the Safety Follow-up Period, for subjects who discontinue prematurely from the study and have not withdrawn consent (or had consent withdrawn by LAR) from further data collection, a telephone call to the subject and/or study partner/caregiver to confirm that the subject is still living will be conducted 30 (+4) days after the subject's intended day of last dose of study drug (i.e., the day that their last dose of study drug would have been taken had they not

	discontinued prematurely). If a subject has died in this follow-up period, every effort will be made where possible to collect the cause of death. **End of Study** For subjects enrolling into Study ACP-204-008, a subject is considered to have completed this study if he/she has completed the EOT visit for Part 1 or Part 2A or Part 2B of this study and has not had an ET from the study. For subjects not enrolling into Study ACP-204-008, a subject is considered to have completed this study if he/she has completed all visits, including the Safety Follow-up visit at 30 (+4) days after the last dose of study drug, for Part 1 or Part 2A or Part 2B of the study. **Data and Safety Monitoring Board** An independent data and safety monitoring board (DSMB) will review safety information on a regular basis throughout the study.
Study duration for Part 1, Part 2A, and Part 2B	For each separately and independently enrolling study part, the duration of participation for individual study subjects who complete the study will be up to 17 weeks, consisting of a Screening Period of up to 7 weeks, a 6-week Double-blind Treatment Period, and a Safety Follow-up Period of 30 (+4) days for those subjects who do not enroll in the OLE study (Figure S–1). In the case of subjects who discontinue prematurely from the study, the duration of participation will also be up to 17 weeks due to the follow-up telephone call 30 (+4) days after their intended day of last dose of study drug to collect mortality data during Mortality Follow-up (Figure S-2). The study start date is defined as the date the first subject is consented. The primary completion date is the last date that subject data are collected for the primary outcome measure. The study completion date is defined as the last date that subject data are collected, which includes the safety follow-up telephone calls and telephone call for mortality follow-up for subjects who have discontinued prematurely.
Criteria for inclusion and exclusion for Part 1, Part 2A, and Part 2B	For each study part, to be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria:** 1. Is a male or female ≥55 and ≤95 years of age at the time of consent and living in the community or, if permitted by local regulations, in an institutionalized setting 2. Can understand the nature of the study and protocol requirements and provide written informed consent. If the

	subject is deemed not competent to provide informed consent, the following requirements for consent must be met: a. The subject's LAR (or study partner/caregiver, if local regulations allow) must provide written informed consent. b. The subject must provide written (if capable) informed assent per local regulations. 3. Meets clinical criteria for possible or probable Alzheimer's disease (AD) based on the 2011 National Institute on Aging-Alzheimer Association (NIA-AA) criteria (Appendix A) 4. Has either a BBM (at Screening assessment or historical) OR documented/historical evidence such as positron emission tomography or a cerebrospinal fluid biomarker, indicating amyloid plaque deposition and neuropathologic change consistent with Alzheimer's disease as described in the 2018 NIA-AA Research Framework (Jack et al. *Alzheimers Dement.* 2018;14(4):535-562) 5. Meets the revised criteria for psychosis in major or mild neurocognitive disorder established by the International Psychogeriatrics Association (Appendix B) 6. Has an MMSE score ≥6 and ≤24 at Screening and Visit 2 (Baseline) 7. Has sufficient verbal ability to understand and answer questions and comply with procedures, with corrective measures such as hearing aids and reading glasses if necessary, and is willing and able to participate in all scheduled evaluations and complete all required tests 8. Has had psychotic symptoms for at least 2 months prior to Screening 9. Has the following scores at Screening and Visit 2 (Baseline): a. NPI (subjects with an unpaid caregiver such as family or friend) or NPI-NH (subjects with a paid caregiver) Hallucinations Domain score ≥6 (Frequency×Severity) or Delusions Domain score ≥6 (Frequency×Severity) or Psychosis score (Hallucinations plus Delusions Domains scores) ≥9 AND b. CGI-S-ADP score ≥4 10. Lives in a stable place of residence prior to Screening, and there are no plans to change living arrangements before the

	end of the Safety Follow-up Period 11. Has a designated study partner/caregiver (e.g., family member, social worker, case worker or nurse) who meets the following requirements: a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug b. Is fluent in the local language in which study assessments will be administered c. Agrees to participate in study assessments and provides written consent to participate in the study 12. Can complete all study visits with a study partner/caregiver 13. Has a prior magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain (completed within past 3 years from Screening start) taken during or subsequent to the onset of dementia that is consistent with the diagnosis of AD in the Investigator's judgement. If not available, a non-contrast brain MRI or non-contrast head CT must be done during Screening. 14. If the subject is taking a cholinesterase inhibitor, memantine, or both: a. the dose of the medication(s) must be stable for at least 12 weeks prior to Visit 2 (Baseline) and there must be no current plan to change the dose during the course of this study; OR b. if the medication(s) was discontinued, the discontinuation must have occurred no fewer than 2 weeks prior to Visit 2 (Baseline). 15. If the subject is taking an antipsychotic medication at the time of Screening, the antipsychotic must be completely discontinued by 3 days prior to Visit 2 (Baseline) (i.e., no antipsychotic dose during the 3 days prior to the day of the Baseline visit) as determined by the Investigator in discussion with the Medical Monitor. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well -controlled or the subject cannot tolerate the current medication). 16. Must have a negative COVID-19 diagnostic test (polymerase chain reaction [PCR], rapid antigen, or transcription mediated amplification) at Screening; must not be planning to receive a COVID-19 vaccine during the

	study or within 30 days of the last dose of study drug. 17. If the subject is a female, she must be of nonchildbearing potential, defined as either surgically sterilized (bilateral tubal occlusion, oophorectomy, or salpingectomy; or hysterectomy) or at least 1 year postmenopausal. 18. If the subject is male and sexually active, he must use a condom (unless he is vasectomized) from the time of consent until 90 days after the last dose of study drug. If the male subject's female partner is of childbearing potential, she must use a barrier contraceptive method (e.g., condom, diaphragm) plus spermicide or a highly effective method of contraception. Highly effective methods of contraception include: combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, or transdermal) associated with inhibition of ovulation; progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; intrauterine device (IUD); and intrauterine hormone releasing system. Male subjects must agree to not donate sperm from the time of Screening until 90 days after the last dose of study drug. **Exclusion Criteria:** 1. Is in hospice and receiving end-of-life palliative care, or has become bedridden 2. Requires skilled nursing care (procedures that can only be administered by a registered nurse or doctor, such as but not limited to, intravenous administration of medication, procedures related to insertion or care of suprapubic catheters, and nasopharyngeal/tracheostomy aspiration) 3. Has psychotic symptoms that are primarily attributable to delirium, substance abuse, or a medical or psychiatric condition (e.g., schizophrenia, bipolar disorder, delusional disorder) other than dementia 4. Has had a major depressive episode within 3 months of Screening, according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria 5. Is actively suicidal at Screening or Visit 2 (Baseline), including an answer of "yes" to the Columbia–Suicide Severity Rating Scale (C-SSRS) questions 4 or 5 (current or over the last 6 months), or has attempted suicide in the 2 years prior to Screening 6. Has a GCAS score of 3 or 4 based on Investigator's assessment of behavior within the 3 months prior to Screening or since last visit at Visit 2 (Baseline) 7. Has evidence of a non-neurologic medical comorbidity or

	medication use that could substantially impair cognition 8. Has a history of ischemic or hemorrhagic stroke within the last 12 months with evidence of residual motor or sensory impairment 9. Has a known history of cerebral amyloid angiopathy, epilepsy, central nervous system (CNS) neoplasm, or unexplained syncope 10. Has atrial fibrillation unless adequately anticoagulated 11. Has symptomatic orthostatic hypotension including symptoms such as postural dizziness or pre-syncope, as measured by UKU orthostatic dizziness severity greater than zero, or history of falls associated with orthostatic hypotension, at Screening or Baseline 12. Has any of the following: a. greater than New York Heart Association Class II congestive heart failure (Appendix C) b. Grade II or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale) (Appendix D) c. sustained ventricular tachycardia d. ventricular fibrillation e. torsade de pointes f. syncope due to an arrhythmia g. an implantable cardiac defibrillator 13. Had a myocardial infarction within the 6 months prior to Screening 14. Has a known personal or family history or symptoms of long QT syndrome 15. Has any of the following 12-lead ECG results at Screening (triplicate ECG) or Visit 2 (Baseline, single ECG): a. If the subject is not on citalopram, escitalopram, or venlafaxine: i. QTcF >450 ms, if QRS duration <120 ms ii. QTcF >470 ms, if QRS duration ≥120 ms b. If the subject is on citalopram, escitalopram, or venlafaxine: i. QTcF >425 ms, if QRS duration <120 ms ii. QTcF >450 ms, if QRS duration ≥120 ms If the mean QTcF value from the set of three ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening by agreement with the Medical Monitor. In this case, the repeat set of triplicate ECGs will be used in determination of

	subject eligibility. 16. Has a heart rate <50 beats per minute, as measured by vital signs. If bradycardia is secondary to iatrogenic or treatable causes and these causes are addressed, a heart rate assessment can be repeated during the Screening Period. 17. Has a significant unstable medical condition that could interfere with subject's ability to complete the study or comply with study procedures 18. Has a clinically significant laboratory abnormality at Screening that, in the judgment of the Investigator or Medical Monitor, will either jeopardize the safe participation of the subject in the study or interfere with the conduct or interpretation of safety or efficacy evaluations in the study 19. Has any of the following laboratory results at Screening: a. Platelets ≤75,000/mm^3 b. Hemoglobin ≤9.5 g/dL if male, or ≤8.5 g/dL if female c. Neutrophils, absolute ≤1000/mm^3 d. Aspartate aminotransferase (AST) >2×upper limit of normal e. Alanine aminotransferase (ALT) >2×upper limit of normal f. Creatinine ≥2 mg/dL g. Hemoglobin A1c (HbA1c) ≥8.5% h. Abnormal free thyroxine (T4) i. Vitamin B12 deficiency j. estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 Laboratory testing may be repeated during Screening by agreement with the Medical Monitor. The repeat results will be used in determination of subject eligibility. 20. Known history of infection with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV). Subjects with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen. Subjects with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test. 21. Has other clinically significant CNS abnormalities that are most likely contributing to the dementia or findings on MRI or CT including: a. intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral

	edema] or glioma) b. vascular malformation c. intracranial aneurysm >4 points by PHASES score (Appendix E) d. evidence of >4 hemosiderin deposits (definite microhemorrhage or superficial siderosis) 22. Requires treatment with a medication or other substance that is prohibited by the protocol or will be used in a way that violates a use restriction (Appendix F and Appendix G), or has been treated with anti-tau therapy or amyloid beta-directed monoclonal antibodies less than 5 half-lives prior to Screening (e.g., aducanumab within 4 months prior to Screening, lecanemab within 4 weeks prior to Screening, or donanemab within 2 months prior to Screening). Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication). 23. Has a BMI <18.5 kg/m^2 or known unintentional weight loss ≥7% of body weight over past 6 months 24. The urine toxicology screen result at Screening indicates the presence of amphetamine/ methamphetamine, barbiturates, cocaine, ecstasy (MDMA), or phencyclidine (PCP). Subjects who test positive and have a valid prescription for amphetamines or barbiturates may be retested during Screening if they agree to abstain from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (Baseline). The repeat screening test must be negative for them to participate in the study. The presence of alcohol, benzodiazepines, marijuana (THC), or opiates will not necessarily exclude the subject from the study, and eligibility will be further evaluated by the Medical Monitor on a case-by-case basis. 25. Has major surgery planned between Screening and the end of the Safety Follow-up Period 26. Has participated in or is participating in a clinical study of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 1a (Screening) OR has participated in a clinical study for disease-modifying therapy within 6 months of Visit 1a 27. Has previously been enrolled in any prior clinical study with ACP-204 or is currently taking ACP-204

	28. Has a significant sensitivity or allergic reaction to ACP-204 or its excipients 29. Has a history of non-response to pimavanserin treatment 30. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. 31. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason
Pharmacokinetic assessments	PK samples will be collected at Weeks 0, 2, 4, and 6 from subjects in all parts of the study. Pharmacokinetic samples will also be collected, if possible, immediately following any serious adverse event (SAE) or any adverse event (AE) leading to discontinuation. For all post-baseline PK samples (scheduled and unscheduled), the dates and times of administration of the last three doses of study drug should be recorded, as well as the date and time of the sample draw. The baseline PK sample will be taken predose.
Biomarkers assessments	For subjects in all parts of the study, blood samples will be collected for testing biomarkers for Alzheimer's disease at Visit 1a (Screening) and for testing additional biomarkers for Alzheimer's disease at Visit 2 (Baseline).
Sample size calculations for Part 1, Part 2A, and Part 2B	**Part 1:** In Part 1, approximately 318 subjects will be randomized in a 1:1:1 ratio to ACP-204 60 mg (n=106), ACP-204 30 mg (n=106), or placebo (n=106). After allowance of 5% non-evaluable subjects, at least 100 evaluable subjects will be randomized per treatment group. This will provide at least 80% power to detect a standard effect size 0.4 between either ACP-204 dose (n=100) and placebo (n=100) at an alpha level of 0.05 using a two-sided test. **Part 2A and Part 2B:** In each of Part 2A and Part 2B of the study, approximately 378 subjects will be randomized in a 1:1:1 ratio to ACP-204 60 mg (n=126), ACP-204 30 mg (n=126), or placebo (n=126), to include at least 360 evaluable subjects after allowance of 5% non-evaluable subjects. These 360 subjects, with two active ACP-204 doses should provide at least 85% power to detect a standard effect size 0.4 between either ACP-204 dose (n=120) and placebo (n=120) at an alpha level of 0.05 using a two-sided test.

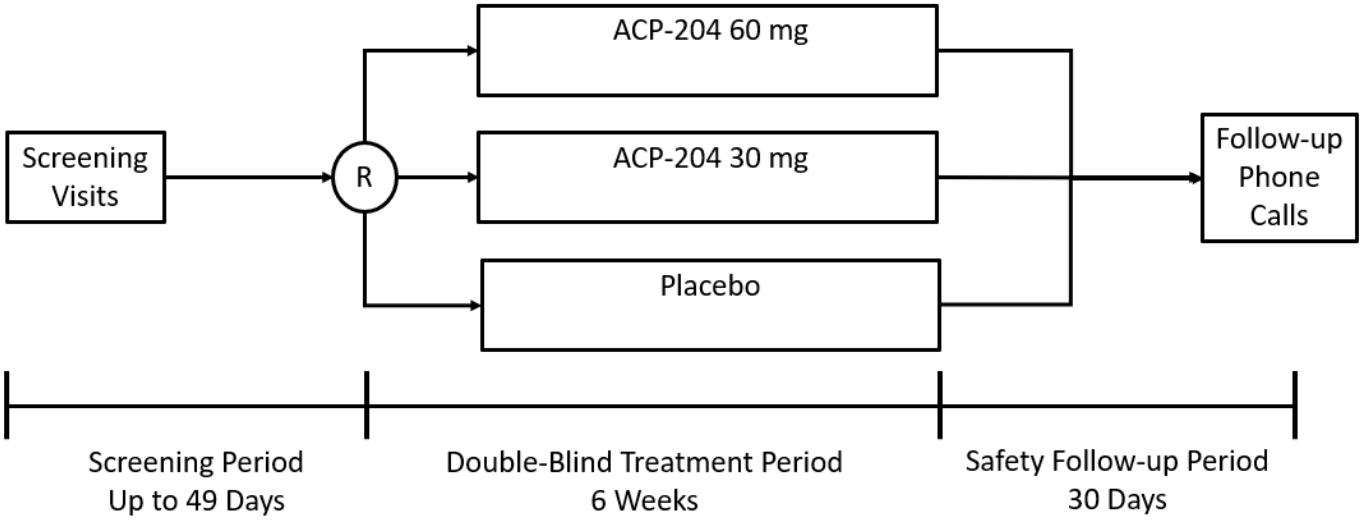
Statistical methods for Part 1, Part 2A, and Part 2B	**Analysis Sets** Part 1 of Study ACP-204-006 will be locked, unblinded, and analyzed while Part 2A and Part 2B are ongoing. Part 2A and Part 2B will be analyzed independently from each other and independently from the Part 1 analysis. The Randomized Analysis Sets of Part 1, Part 2A, and Part 2B include all subjects who were randomized in Part 1, Part 2A, or Part 2B, respectively. The Randomized Analysis Sets will be used for analyses specified in the SAP based on the randomized treatment assignment. The Safety Analysis Sets of Part 1, Part 2A, and Part 2B include all randomized subjects in Part 1, Part 2A, or Part 2B, respectively, who received at least one dose of study drug (ACP-204 or placebo). Subjects will be analyzed based on the treatment they actually received. The Safety Analysis Sets will be used for all safety analyses. The Full Analysis Sets of Part 1, Part 2A, and Part 2B include all randomized subjects in Part 1, Part 2A, or Part 2B, respectively, who received at least one dose of study drug and who have both a baseline value and at least one post-baseline value for SAPS-H+D total score. Subjects will be analyzed based on their planned randomized treatment. The Full Analysis Sets will be used for the analysis of all efficacy endpoints. The PK Analysis Set includes all subjects in the Safety Analysis Set who have sufficient PK data to derive at least one PK parameter. **Subgroup Analysis** Selected analyses may be performed in subgroups defined in the statistical analysis plan (SAP). **Descriptive Statistics** Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For each

	categorical outcome, the number and percentage of subjects in each category will be reported. **Missing Data** Handling of missing values will be described in detail in the SAP. Sensitivity analyses will be performed to assess the impact of missing data on the robustness of primary analysis results. **EFFICACY ANALYSES** All efficacy endpoints will be analyzed and summarized by treatment group using the Full Analysis Set of Part 1 and the Full Analysis Sets of independent Part 2A and Part 2B, respectively. The Full Analysis Sets of Part 2A and Part 2B will be analyzed separately from each other and independently from the Full Analysis Set of Part 1. All efficacy endpoints will be summarized by treatment group using descriptive statistics. **Primary Efficacy Analysis** Change from Baseline in SAPS-H+D total score will be analyzed using the mixed-effect model repeated measures (MMRM). The model will include effects for treatment groups, visit, treatment-by-visit interaction, baseline SAPS-H+D total score-by-visit interaction, and randomization stratification factors (site, institution status [yes or no]). An unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The treatment effect will be estimated by the difference in least squares means at Week 6 and will be tested at an alpha level of 0.05 (two-sided) using the Full Analysis Set of Part 1 and Full Analysis Sets of Part 2A and Part 2B, respectively. The difference in least squares means, corresponding 95% confidence interval and p-value will be reported. **Key Secondary Efficacy Analysis** The key secondary efficacy endpoint, CGI-I-ADP score at Week 6, will be analyzed in a similar fashion as the primary endpoint. The model will include effects for treatment groups, visit, treatment-by-visit interaction, randomization stratification factors (site, institution status [yes or no]), baseline CGI-S-ADP score, and baseline CGI-S-ADP score-by-visit interaction. The treatment effect will be estimated by the difference in least squares means of CGI-I-ADP score at Week 6 and will be tested at an alpha level of 0.05 (two-sided) using the Full Analysis Set of Part 1 and Full Analysis Sets of Part 2A and Part 2B, respectively. The difference in least squares means, corresponding 95% confidence interval, and p-value will be reported.

	In order to control the overall type I error rate, the multiplicity will be adjusted for multiple comparisons of 30 mg versus placebo and 60 mg versus placebo for the primary endpoint and key secondary endpoint. Details of the multiplicity control procedure will be provided in the SAP. **Other Secondary and Exploratory Efficacy Analyses** For analysis of continuous efficacy endpoints, the analysis method will be the same as that used for the primary variables, except for QOL-AD score and SDI score. The QOL-AD score and SDI score will be analyzed using analysis of covariance. For analysis of categorical variables in other secondary efficacy endpoints (e.g., proportional analysis), the Cochran Mantel Haenszel approach stratified by the randomization strata will be used. All other (i.e., not key) secondary and exploratory efficacy analyses will be performed using the Full Analysis Set of Part 1 and Full Analysis Sets of Part 2A and Part 2B, respectively. **SAFETY ANALYSES** All safety analyses will be performed using the Safety Analysis Set of Part 1 and Safety Analysis Sets of Part 2A and Part 2B, respectively. Safety results will be summarized by treatment group using descriptive statistics. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities. All AEs will be listed, and TEAEs will be summarized by system organ class and preferred term. Treatment-emergent adverse events, TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, serious TEAEs, and serious TEAEs related to study drug will all be summarized. Adverse events of special interest (AESIs) will be summarized as well. Deaths of subjects who discontinue prematurely from the study that occur between 30 days after the last dose of study drug and 30 days after the subject's intended day of last dose of study drug will be summarized separately. Descriptive statistics for ECG, vital signs and weight, and clinical laboratory parameters, including change from Baseline, will be tabulated by visit and treatment group. The results of the physical examinations at each visit will be tabulated by treatment group. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation guidelines and based on the Food and Drug Administration E14 Guidance Document. The incidence of clinically significant changes in selected laboratory parameters will also be summarized.

	UKU Sleepiness/Sedation and Orthostatic Dizziness, MMSE, DSST, and ESRS-A scores and changes from Baseline will be summarized by treatment group and visit and will be analyzed using an MMRM model similar to the primary analysis. For the GCAS, the number and percentage of subjects with a score of 3 or 4 during the study will be tabulated. For the C-SSRS, the summary descriptive statistics will be tabulated. An independent DSMB will review safety information on a regular basis throughout the study. **Pharmacokinetic (PK) Analyses** Plasma concentration data for ACP-204 will be listed and summarized using descriptive statistics. Results will be used for other analyses (e.g., population PK and PK/PD modeling), which will be presented in a separate report(s). **Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses** Guided by exploratory analyses, PK/PD models to describe the exposure-response relationship between ACP-204 exposure parameters and the relevant efficacy and safety endpoints will be developed using appropriate PK/PD methods. Results will be presented in a separate report per a prespecified data analysis plan.
Date	15 October 2024

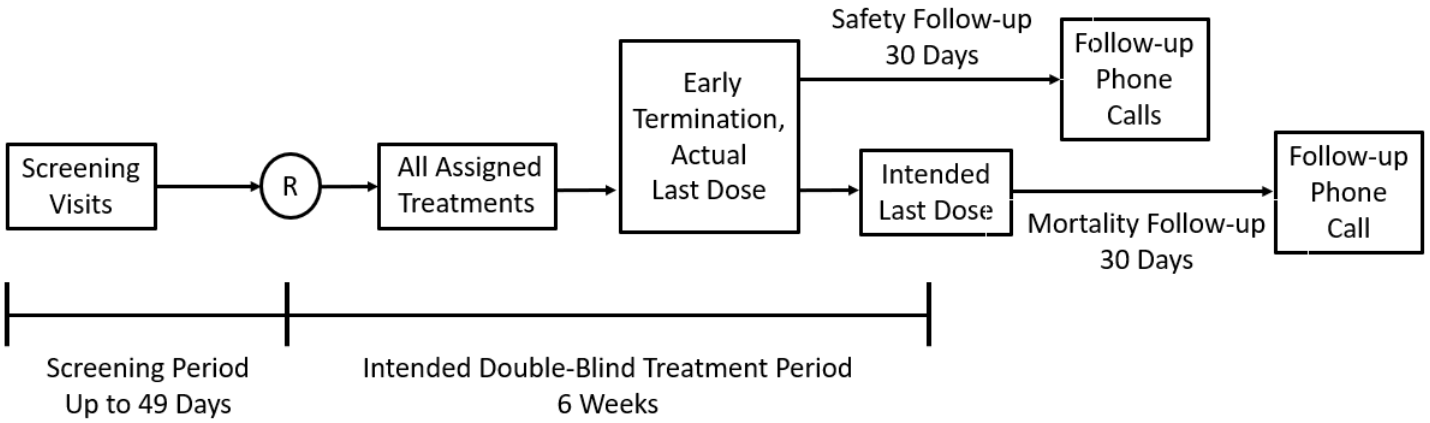
Figure S–1 Schematic of Study Design for ACP-204-006 – Subjects Completing the Study in Part 1, Part 2A, and Part 2B



Abbreviations: R=randomization

Note: Subjects who enroll in the open-label extension study will not complete the Safety Follow-up Period. For completing subjects who do not enroll in the open-label extension study, there will be two telephone calls during the Safety Follow-up Period, one at 7 (±3) days and another at 30 (+4) days after the last dose of study drug.

Figure S-2 Schematic of Study Design for ACP-204-006 – Subjects Early Terminating in Part 1, Part 2A, and Part 2B



Abbreviations: R=randomization

Note: Subjects who terminate early will have three follow-up telephone calls, two during the Safety Follow-up Period (one at 7 [±3] days and another at 30 [+4] days after the last dose of study drug), and another for Mortality Follow-up 30 (+4) days after the subject's intended day of last dose of study drug (i.e., the day that their last dose of study drug would have been taken had they not discontinued prematurely).

Table S–1 Schedule of Events and Assessments for ACP-204-006 in Part 1, Part 2A, and Part 2B

Period	Screening		Double-blind Treatment Period					Safety Follow-up[a]		Mortality Follow-up[o]
Visit day/Week	Day -49 or later		Week 0	Week 1	Week 2	Week 4	Week 6	Visit 6 +7 days	Visit 6 +30 days	Week 6 +30 days
Visit number	1a	1b	Baseline 2	3	4	5	(EOT/ET) 6	7	8	9
Visit window (days)				±3	±3	±3	±3	±3	+4	+4
Type of visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call	Phone call	Phone call
Informed consent/assent	X[s]						X[p]			
Inclusion/exclusion criteria		X	X							
Clinical Validation Inventory for Study Admission		X								
Medical history and demographics		X								
Psychiatric, dementia, and neurological history		X								
Physical and neurological examination		X	X				X			
Brief Psychosocial Therapy		X[q]								
Vital signs (including orthostatic changes)[b] and weight		X	X	X	X	X	X			
Assessment of peripheral edema		X	X	X	X	X	X			
Height		X								
12-lead ECG[c]		X	X	X	X	X	X			
Clinical laboratory tests[d]	X		X[n]		X		X			
Biomarkers for Alzheimer's disease for eligibility blood sampling	X									
Urine toxicology screen[e]	X		X				X			
COVID-19 test[f]	X									
MMSE		X	X	X	X	X	X			

Table continued on next page.

Table S–1 Schedule of Events and Assessments for ACP-204-006 in Part 1, Part 2A, and Part 2B (Continued)

Period	Screening		Double-blind Treatment Period					Safety Follow-up[a]		Mortality Follow-up[o]
Visit day/Week	Day -49 or later		Week 0	Week 1	Week 2	Week 4	Week 6	Visit 6 +7 days	Visit 6 +30 days	Week 6 +30 days
Visit number	1a	1b	Baseline 2	3	4	5	(EOT/ET) 6	7	8	9
Visit window (days)				±3	±3	±3	±3	±3	+4	+4
Type of visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call	Phone call	Phone call
DSST		X	X	X	X	X	X			
SAPS-H+D		X	X	X	X	X	X			
NPI or NPI-NH[g]		X	X		X	X	X			
NPI-C hallucinations and delusions domains[h]		X	X		X	X	X			
CGI-S-ADP		X	X	X	X	X	X			
CGI-I-ADP				X	X	X	X			
GCAS[i]		X	X	X	X	X	X	X	X	
C-SSRS[i]		X	X	X	X	X	X	X	X	
ESRS-A			X	X	X	X	X			
QOL-AD			X				X			
EQ-5D-5L[j]							X			
UKU Sleepiness/Sedation and Orthostatic Dizziness		X	X	X	X	X	X			
SDI			X				X			
Brain MRI or CT[k]		X								
Assessment of concomitant (or post-treatment) medications/procedures	X	X	X	X	X	X	X	X[l]	X[l]	
Assessment of adverse events	X	X	X	X	X	X	X	X	X	
Randomization			X							
Dispense study drug			X		X	X				

Table continued on next page.

Table S–1 Schedule of Events and Assessments for ACP-204-006 in Part 1, Part 2A, and Part 2B (Continued)

Period	Screening		Double-blind Treatment Period					Safety Follow-up[a]		Mortality Follow-up[o]
Visit day/Week	Day -49 or later		Week 0	Week 1	Week 2	Week 4	Week 6	Visit 6 +7 days	Visit 6 +30 days	Week 6 +30 days
Visit number	1a	1b	Baseline 2	3	4	5	(EOT/ET) 6	7	8	9
Visit window (days)				±3	±3	±3	±3	±3	+4	+4
Type of visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call	Phone call	Phone call
Study drug accountability				X	X	X	X			
Additional biomarkers for Alzheimer's disease blood sampling			X							
Pharmacokinetics blood sampling[m]			X		X	X	X			
Optional exit interview with caregiver (US sites only)								X[r]		
Vital status										X

Abbreviations: ADP=Alzheimer's disease psychosis; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BPST=brief psychosocial therapy; CGI-I=Clinical Global Impression–Improvement; CGI-I-ADP=Clinical Global Impression–Improvement in the ADP context; CGI-S=Clinical Global Impression–Severity; CGI-S-ADP=Clinical Global Impression–Severity in the ADP context; COVID-19=coronavirus disease 2019; C-SSRS=Columbia–Suicide Severity Rating Scale; CT=computed tomography; DSST=Digit Symbol Substitution Test; ECG=electrocardiogram; eCRF=electronic case report form; EOT=end of treatment; EQ-5D-5L=5-level version of EuroQol-5D; ESRS-A=Extrapyramidal Symptom Rating Scale–Abbreviated; ET=early termination; GCAS=Global Clinician Assessment of Suicidality; LAR=legally acceptable representative; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI=Neuropsychiatric Inventory; NPI-C=Neuropsychiatric Inventory–Clinician; NPI-NH=Neuropsychiatric Inventory–Nursing Home Version; OLE=open-label extension; PCR=polymerase chain reaction; QOL-AD=Quality of Life in Alzheimer's Disease; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales; SAE=serious adverse event; SDI=Sleep Disorders Inventory; UKU=Udvalg for kliniske undersøgelser

Note: Every effort should be made to complete each visit in a single day, with the exception of Screening visits. However, if the subject has documented/historical evidence indicating amyloid plaque deposition and neuropathologic change consistent with Alzheimer's disease, then the procedures for Screening Visits 1a and 1b may occur on the same day. In the event of a split visit during Screening or the Double-blind Treatment Period, completion of the CGI-S/CGI-I and the SAPS-H+D on the same day should be prioritized.

[a] This Safety Follow-up Period includes two telephone calls (each to the subject and study partner/caregiver) for subjects who discontinue prematurely from the study, or who complete the treatment period of the study and do not rollover into the open-label extension study. These telephone calls will occur at 7 (±3) days and 30 (+4) days after the last dose of study drug, provided the subject or LAR has not withdrawn consent from further data collection.

[b] Vital signs will include body temperature, resting respiration rate, and orthostatic blood pressure (systolic and diastolic) and pulse rate. Blood pressure and pulse rate will be measured after the subject rests for 5 minutes in the supine position. The subject will then be asked to stand, and blood pressure and pulse

rate will be taken after standing for approximately 1 minute and then again after the subject has been standing for approximately 3 minutes (no later than 5 minutes). Subjects unable to stand may be assessed while sitting upright. The same position and arm should be used each time vital signs are measured for a given subject. Orthostatic hypotension is defined as a decrease in systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg after transitioning from the supine position (after resting for 5 minutes) to standing after 1 or 3 minutes. If orthostatic hypotension is present, the Investigator should determine if the subject has associated symptoms such as postural dizziness or pre-syncope, as measured by UKU orthostatic dizziness severity greater than zero, or history of falls associated with orthostatic hypotension. If a subject with orthostatic hypotension at Screening or Baseline has associated symptoms, this will be exclusionary.

[c] The 12-lead ECG will be completed in triplicate at Screening. A single ECG will be completed at all other visits. The ECG should be completed before or at least 30 minutes after any blood sampling.

[d] Except for when required for eligibility, if collection of a urine sample for clinical laboratory tests (urinalysis) proves impractical or impossible, failure to collect a urine sample should be recorded in the subject's eCRF and will not be considered a protocol deviation.

[e] If after Screening collection of a urine sample for urine toxicology screen proves impractical or impossible, controlled substances and alcohol will be tested from a blood sample where local regulations permit this. Where testing from a blood sample cannot be performed, this will not be considered a protocol deviation for testing after enrollment. However, for eligibility, testing for controlled substances and alcohol in urine (not blood) must be performed.

[f] The COVID-19 test will be a PCR, rapid antigen, or transcription mediated amplification test at Screening.

[g] For this study, the NPI version will be utilized for subjects with an unpaid caregiver such as family or friend, and the NPI-NH will be utilized for those with a paid caregiver.

[h] When the necessary materials and resources become available/approved at their clinic, subjects who can begin this assessment at their Screening visit should undergo the NPI-C assessment. The NPI-C should not be first implemented with any subject at their Baseline visit or later.

[i] Global Clinical Assessment of Suicidality–Screening Version will be used at Screening. GCAS-Since-Last-Visit Version will be administered at Baseline (Visit 2) and used thereafter in the study. The Baseline/Screening version of the C-SSRS will be administered at Screening, and the "Since Last Visit" version will be administered at Baseline and at all other designated visits.

[j] For subjects who enroll in the OLE study, EQ-5D-5L will be assessed at the EOT visit in this study, as this assessment will serve as the baseline EQ-5D-5L assessment for the OLE study.

[k] A non-contrast brain MRI or non-contrast head CT should only be completed if a MRI or CT scan has not been performed in the last 3 years prior to Screening AND during or subsequent to the onset of Alzheimer's disease.

[l] Post-treatment medications and procedures will be assessed.

[m] One PK sample will be collected at each indicated visit. Pharmacokinetic samples will also be collected, if possible, immediately following any SAE or any AE leading to discontinuation. For each individual subject, the PK samples collected at Weeks 2, 4, and 6 (i.e., postdose samples) should be collected at times that vary as much as possible between 2 and 24 hours after dosing within prespecified time intervals. One sample should be collected 2-5 hours after dosing, one sample should be collected 5-8 hours after dosing, and one sample should be collected 8-24 hours after dosing. If this is not possible and samples at two different visits must be collected within the same time interval after dosing, then these should vary within the interval to provide as much variation as possible overall.

[n] Results at Baseline for platelets, hemoglobin, neutrophils, AST, ALT, and creatinine that would be exclusionary at Screening will result in ET, but enrollment of the subject will not be considered a protocol deviation. Likewise, ET for any clinically significant laboratory abnormality at Baseline will not be considered a protocol deviation.

[o] In addition to the safety follow-up telephone calls during the Safety Follow-up Period, for subjects who discontinue prematurely from the study and have not withdrawn consent (or had consent withdrawn by LAR) from further data collection, a telephone call to the subject and/or study partner/caregiver to confirm that the subject is still living (i.e., vital status) will be conducted 30 (+4) days after the subject's intended day of last dose of study drug (i.e., the day that their last dose of study drug would have been taken had they not discontinued prematurely).

[p] For subjects who enroll in the OLE study, subject consent/assent and study partner/caregiver consent for the OLE study must be obtained per local regulations prior to the procedures being performed at the EOT visit in this study, as these EOT procedures will serve as the baseline procedures for the OLE study.

[q] Study partners/caregivers will be instructed on the BPST by trained site personnel and will have approximately weekly supportive telephone contacts.

[r] The optional exit interview with caregiver will be administered by third-party trained interviewers by telephone/web-based audio within approximately 2 weeks after an EOT or ET visit only at US sites for caregivers who provide separate informed consent for this optional interview. It does not have to be performed on the same day as the safety follow-up telephone call that is nominally 7 days after Visit 6 (EOT/ET).

[s] As part of the informed consent process, the informed consent form (ICF) for the optional caregiver exit interview will be provided to all caregivers at US sites. Consent may be obtained at any applicable study visit, but it must be obtained no later than Visit 6 (EOT/ET).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
5-HT_{2A} receptor	5-hydroxytryptamine (serotonin) receptor subtype 2A
AD	Alzheimer's disease
ADP	Alzheimer's disease psychosis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BBM	blood biomarker
BMI	body mass index
BP	blood pressure
BPST	brief psychosocial therapy
CGI-I	Clinical Global Impression–Improvement
CGI-I-ADP	Clinical Global Impression–Improvement in the ADP context
CGI-S	Clinical Global Impression–Severity
CGI-S-ADP	Clinical Global Impression–Severity in the ADP context
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	creatinine
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
CYP3A4	cytochrome P450 3A4 enzyme
DRP	dementia-related psychosis
DSMB	data and safety monitoring board
DSST	Digit Symbol Substitution Test
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EQ-5D-5L	5-level version of EuroQol-D
ESRS-A	Extrapyramidal Symptom Rating Scale–Abbreviated
ET	early termination
EU GDPR	European Union General Data Protection Regulation

Term	Definition
FDA	Food and Drug Administration
GCAS	Global Clinician Assessment of Suicidality
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IRT	interactive response technology
LAR	legally acceptable representative
MMRM	mixed-effect model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NPI	Neuropsychiatric Inventory
NPI-C	Neuropsychiatric Inventory–Clinician
NPI-NH	Neuropsychiatric Inventory–Nursing Home Version
OLE	open-label extension
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
PP	per-protocol
PR	PR interval on ECG
QD	once daily
QOL	quality of life
QOL-AD	Quality of Life in Alzheimer's Disease
QRS	QRS interval on ECG
QT	QT interval on ECG
QTc	corrected QT interval on ECG
QTcB	corrected QT interval using Bazett's correction method
QTcF	corrected QT interval using Fridericia's correction method
SAE	serious adverse event
SAP	statistical analysis plan
SAPS	Scale for the Assessment of Positive Symptoms
SAPS-H+D	SAPS–Hallucinations and Delusions subscales
SDI	Sleep Disorders Inventory
T4	thyroxine
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack

Term	Definition
TSH	thyroid-stimulating hormone
UKU	Udvalg for kliniske undersøgelser

1 INTRODUCTION

This document is a research protocol and the described study will be conducted in compliance with the protocol, the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) Guideline, and applicable regulatory requirements.

1.1 Background Information

Alzheimer's disease (AD) is the most common and well-known cause of dementia. Psychosis is common in various types of dementia, with the prevalence of hallucinations and delusions in AD reported to be 18% and 36%, respectively (Jellinger 2012), and other studies also indicating that among AD patients, delusions are more common than hallucinations (Ballard et al. 1995; Fischer et al. 2016).

Dementia-related psychosis (DRP) differs substantially from schizophrenia, mania with psychotic features, major depressive disorder with psychotic features, and other major mental illnesses. Because of these differences, the assessment of psychosis in dementia is focused on a narrow set of symptoms (e.g., hallucinations and delusions) distinct from schizophrenia (Jeste and Finkel 2000; Cohen-Mansfield and Golander 2011).

Treatment of DRP, and Alzheimer's disease psychosis (ADP) specifically, represents an area of high unmet need. Clinical experience and clinical trial data with atypical antipsychotics have consistently shown treatment effects across the spectrum of all neurodegenerative dementias (Devanand et al. 1998; De Deyn et al. 1999; Katz et al. 1999; Street et al. 2000; Devanand et al. 2012). However, the CATIE-AD study (in patients with AD) concluded that the adverse effects of risperidone, olanzapine, and quetiapine offset their advantages in efficacy. Although the atypical antipsychotic drugs were more effective than placebo, adverse effects limited their overall effectiveness. The authors stated that use of these agents may be restricted to patients who have few or no side effects and for whom benefits can be discerned (Schneider et al. 2006).

1.2 Investigational Product

ACP-204 is a highly potent and selective antagonist/inverse agonist of 5-hydroxytryptamine (serotonin) receptor subtype 2A (5-HT_{2A} receptors). Its only other notable receptor activity is as an antagonist/inverse agonist at 5-HT_{2C} receptors. ACP-204 does not exhibit appreciable activity at dopaminergic, histaminergic, adrenergic, or muscarinic receptors. 5-HT_{2A} inverse agonists/antagonists have the potential to treat several conditions, including schizophrenia, DRP (encompassing ADP), depression, drug relapse, and autism.

Please refer to the current ACP-204 Investigator's brochure for additional information.

1.3 Previous Clinical Experience

As of 19 March 2024, ACP-204 had been evaluated in three completed Phase 1 studies in healthy subjects: a single ascending dose study, ACP-204-001; a single dose and multiple ascending dose study, ACP-204-002; and a positron emission tomography (PET) study, ACP-204-003. ACP-204 has been administered to healthy adult subjects (18 to 55 years of age) as single and multiple ascending doses and to healthy elderly subjects (65 to 75 years of age) as multiple ascending doses.

Efficacy has not yet been assessed, and the data indicate that ACP-204 was well tolerated with no safety signals of concern in any of these three Phase 1 studies.

The pharmacokinetics (PK) of ACP-204 have been assessed following single ascending ACP-204 doses (10 to 180 mg) and multiple ascending ACP-204 doses (10 to 120 mg) in healthy adult subjects and following multiple ascending ACP-204 doses (10 to 60 mg) in healthy elderly subjects. Please refer to the current ACP-204 Investigator's brochure for additional PK information.

Always refer to the latest version of the ACP-204 Investigator's brochure for the overall benefit/risk assessment and the most accurate and current information regarding nonclinical data, drug metabolism, PK, efficacy, and safety.

1.4 Study Rationale

As discussed above, DRP, and specifically ADP, is an area of high unmet need. Currently there is no pharmacologic treatment approved for ADP. Atypical antipsychotics are frequently used to treat this disorder despite significant safety concerns about their use in this population.

This study, ACP-204-006, will be the first clinical study to evaluate both the efficacy and safety of ACP-204 for the treatment of hallucinations and delusions in subjects with ADP. Subjects who complete this study will have the option of participating in the long-term open-label extension (OLE) study, ACP-204-008 (pending confirmation of eligibility), which will further expand the safety database for ACP-204 in patients with ADP.

1.4.1 Rationale for Study Design

ACP-204-006 includes three independent and separately enrolling parts, Part 1 (Phase 2) and Part 2A and Part 2B (Phase 3). The Part 1 (Phase 2) analysis will provide proof-of-concept, as well as dose-finding efficacy and safety information, and then confirmatory efficacy and safety will be provided in Part 2A and Part 2B of the study (Phase 3). Part 2A and Part 2B will be analyzed separately from each other and Part 1. The analyses of Part 1, Part 2A, and Part 2B are each appropriately sized with sufficient power to describe a significant ACP-204 treatment effect over placebo.

Sites will begin work on either Part 2A or Part 2B as soon as their work on Part 1 has ended and before the results of analysis of Part 1 are available. No site will be allowed to work on both Part 2A and Part 2B, and each study part will have an independent randomization scheme. This should ensure that Part 2A and Part 2B are different and independent of each other. The proposed seamless design with no delay between sites ending their work on Part 1 (Phase 2, proof-of-concept and dose-finding) and beginning work on Part 2A or Part 2B (Phase 3, confirmatory efficacy) will considerably reduce drug development timelines.

The primary endpoint of the study is change from Baseline at Week 6 in the Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales (SAPS-H+D) total score. The SAPS-H+D is a well-established measure of two psychotic symptoms, hallucinations and delusions, which are the psychotic symptoms that pimavanserin, a related selective antagonist/inverse agonist of 5-HT_{2A} receptors, effectively treats in the context of Parkinson's disease psychosis (PDP) (NUPLAZID® (pimavanserin) US package insert [Acadia Pharmaceuticals Inc. 2023]). Pimavanserin has also been shown to improve SAPS-H+D scores in a group of patients with DRP that included a large subset of patients with ADP (Tariot et al. 2021).

The 6-week Double-blind Treatment Period is deemed appropriate for evaluating acute antipsychotic efficacy. This duration is also consistent with the literature in ADP and regulatory guidance for evaluation of drugs for treatment of psychosis in schizophrenia (European Medicines Agency 2012; Ballard et al. 2018).

The total number of subjects targeted for randomization will be 318 subjects in Part 1 and 378 subjects in each of Part 2A and Part 2B, with each part having two active treatment groups and a placebo group. There is therefore sufficient power to support the independent analysis of any single study part.

Placebo is used as comparator because there is no approved medication for treatment of hallucinations and delusions in patients with ADP, nor is there any standard of care. Additionally, this study is of short duration, and subjects may be discontinued for lack of efficacy or worsening symptoms.

The study will be randomized with stratification by site, and by whether subjects are living in the wider community or an institution, to balance the number of subjects in the treatment groups and allow fair comparisons within sites and within living situations.

Two assessments of cognition will be used during study drug treatment to monitor any worsening of cognition. Use of the industry standard MMSE will be augmented by use of the DSST, which is more sensitive to slight changes in higher-level cognition than the MMSE.

Two assessments of suicidality will be used in the study: GCAS and C-SSRS. The GCAS will be used because it allows for capture of reports of suicidal behavior in the patient by the study partner or caregiver in subjects with dementia who may not be able to give reliable information in a C-SSRS assessment. The C-SSRS will be used because it allows for mapping to Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories.

In addition to the standard telephone call for safety follow-up at 30 (+4) days after the last dose of study drug (for subjects who discontinue prematurely from the study or do not roll over into the OLE study), a safety follow-up telephone call at 7 (±3) days after the last dose of study drug will occur. This telephone call is timed to detect adverse events (AEs) that might result from having stopped study drug. New and ongoing AEs will be collected.

For subjects who discontinue prematurely from the study, a telephone call to confirm that the subject is still living will be conducted at 30 (+4) days after the subject's intended day of last dose of study drug (i.e., the day that their last dose of study drug would have been taken had they not discontinued prematurely), and if the subject has died, the cause of death will be sought. Because there may be a lag between an AE leading to discontinuation while taking study drug and death resulting from that event, this assessment is included to ensure that all deaths within the intended period of treatment or 30 days thereafter are taken into account.

1.4.2 Rationale for Dose Selection

The proposed doses, 30 mg and 60 mg of ACP-204, have a wide safety margin to no-observed-adverse-effect levels in long term preclinical toxicity studies up to 39 weeks. These doses have been well tolerated in a multiple ascending dose study in the elderly and should provide adequate exposure and brain 5-HT_{2A} receptor occupancy. Acadia anticipates that ACP-204 doses of 30 and 60 mg QD may provide exposures associated with an antipsychotic effect. Further, the proposed doses have been shown to be safe and well tolerated in an elderly population.

Dose selection for the current study is guided by ACP-204 PK profile and safety data following the administration of single doses of ACP-204 up to 180 mg in healthy adult subjects and following multiple doses up to 120 mg in healthy adult subjects and 60 mg in healthy elderly subjects, as well as PET study data and nonclinical pharmacology.

The ACP-204 PK profile is linear/dose proportional, with low to moderate variability, with slightly higher exposure in elderly subjects than in younger adult subjects. The ACP-204 half-life ($t_{1/2}$) is approximately 20 hours, thus establishing once-daily (QD) oral dosing of ACP-204 as an appropriate dosing regimen. In a food-effect study, the criterion for bioequivalence for fed relative to fasted was within the bioequivalence boundary for AUC and C_{max}, and these results indicate that food has no effect on the rate or extent of ACP-204 absorption. ACP-204 was safe and well tolerated over the studied dose range in healthy adult and elderly subjects.

Please refer to the current ACP-204 Investigator's brochure for additional PK and nonclinical pharmacology information.

1.5 Benefit/Risk Assessment

1.5.1 Known Potential Risks

Limited, monitorable, and reversible cardiovascular system effects were seen in monkeys at supratherapeutic doses/exposures in nonclinical ACP-204 safety pharmacology single-dose (consisting of heart rate changes and PR, QRS, and QTc interval prolongations) and repeat-dose toxicity studies (PR and/or QRS interval prolongations). ACP-204 had no effect, at wide margins to the human therapeutic exposure, on the human ether-à-go-go-related potassium channel (HERG) in vitro, a key ion channel regulating cardiac action potential repolarization and the QT interval. Clinical results to date have not raised any concerns about QTc interval prolongation. To mitigate the risk of potential QTc prolongation, the present study has exclusion criteria to ensure that subjects at risk do not participate (Section 4.2).

Nonclinical data indicate that ACP-204 is primarily metabolized by cytochrome P450 3A4 enzyme (CYP3A4). Therefore, moderate and strong CYP3A4 inhibitors and inducers are prohibited or restricted medications in the present study (Appendix G).

Effects in animals associated with ACP-204 included dose and C_{max}-related convulsion-like activity observed in monkeys at supratherapeutic doses/exposures. Sustained convulsion-like activity was seen in a monkey after a 100 mg/kg dose, while in multiple repeat-dose toxicity studies, only one-time convulsion-like episodes were observed in two monkeys at a 40 mg/kg/day dose level. The events seen in repeat-dose studies were considered to occur at supratherapeutic exposure levels and were not considered adverse based on their very sporadic and transient occurrence, as animals recovered without treatment or intervention, and as affected animals had no further observable impact on their overall health and behavior, or notable postmortem central nervous system (CNS) findings.

Please refer to the current ACP-204 Investigator's brochure for additional nonclinical safety information.

1.5.2 Known Potential Benefits

No efficacy data for ACP-204 have been generated in humans. However, data with ACP-204 in animal models of psychosis, as well as ACP-204 having similar pharmacological properties to pimavanserin, a related selective antagonist/inverse agonist of 5-HT_{2A} receptors that effectively treats hallucinations and delusions in the context of PDP (NUPLAZID® [pimavanserin] US package insert [Acadia Pharmaceuticals Inc. 2023]), and which has been shown to improve a measure of hallucinations and delusions in a group of patients with DRP that included a large

subset of patients with ADP (Tariot et al. 2021), provide support for a potential benefit to study subjects with ADP.

Additionally, study subjects may gain satisfaction from contributing to the process of developing a new therapy in an area of unmet need, and they may benefit from medical evaluations/assessments associated with study procedures (e.g., physical exam, electrocardiogram [ECG], clinical laboratory tests).

A detailed summary of the potential benefits is available in the ACP-204 Investigator's brochure.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Efficacy Objectives

The primary efficacy objective for Part 1 is: To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared with placebo in subjects with ADP as measured by the SAPS-H+D total score.

The primary efficacy objective for both Part 2A and Part 2B is: To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared with placebo in subjects with ADP as measured by SAPS-H+D total score.

2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint for Part 1, Part 2A, and Part 2B is: Change from Baseline in the SAPS-H+D total score at Week 6.

2.2 Secondary Efficacy Objectives

2.2.1 Key Secondary Efficacy Objectives

The key secondary efficacy objective for Part 1 is: To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared with placebo in subjects with ADP as measured by Clinical Global Impression–Improvement in the ADP context (CGI-I-ADP).

The key secondary efficacy objective for both Part 2A and Part 2B is: To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared with placebo in subjects with ADP as measured by CGI-I-ADP.

2.2.1.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint for Part 1, Part 2A, and Part 2B is: CGI-I-ADP score at Week 6.

2.2.2 Other Secondary Efficacy Objectives

The other secondary efficacy objective for Part 1 is: To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared to placebo in subjects with ADP in the following domains:

- symptoms of hallucinations and delusions
- sleep disturbance

The other secondary efficacy objective for both Part 2A and Part 2B is: To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared to placebo in subjects with ADP in the following domains:

- symptoms of hallucinations and delusions
- sleep disturbance

2.2.2.1 Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints for Part 1, Part 2A, and Part 2B are:

- CGI-I-ADP score at Weeks 1, 2, and 4
- Change from Baseline on:
  - SAPS-H+D total score at Weeks 1, 2, and 4
  - Sleep Disorders Inventory (SDI) score at Week 6
- Proportion of subjects with:
  - SAPS-H+D total score ≥30% reduction from Baseline, at all visits
  - SAPS-H+D total score ≥50% reduction from Baseline, at all visits
  - SAPS-H+D total score 100% reduction from Baseline or score of 0, at all visits
  - CGI-I-ADP score of 1 (very much improved) or 2 (much improved), at all visits

2.3 Exploratory Efficacy Objectives

The exploratory efficacy objective for Part 1 is: To evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared to placebo in subjects with ADP in the following domains:

- symptoms of hallucinations and delusions
- neuropsychiatric symptoms
- caregiver distress
- occupational disruptiveness
- quality of life (QOL)

The exploratory efficacy objective for both Part 2A and Part 2B is: To evaluate the efficacy of either ACP-204 60 mg or ACP-204 30 mg compared to placebo in subjects with ADP in the following domains:

- symptoms of hallucinations and delusions
- neuropsychiatric symptoms
- caregiver distress
- occupational disruptiveness
- quality of life

2.3.1 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for Part 1, Part 2A, and Part 2B are: Change from Baseline on:

- SAPS Hallucinations domain (SAPS-H) score at all visits
- SAPS Delusions domain (SAPS-D) score at all visits
- Clinical Global Impression–Severity in the ADP context (CGI-S-ADP) score at all visits
- Neuropsychiatric Inventory (NPI) domain and total scores for subjects with an unpaid caregiver such as family or friend OR
  Neuropsychiatric Inventory–Nursing Home Version (NPI-NH) domain and total scores for subjects with a paid caregiver at Weeks 2, 4, and 6
- NPI Caregiver Distress total score for an unpaid caregiver such as family or friend OR NPI-NH Occupational Disruptiveness total score for a paid caregiver at Weeks 2, 4, and 6
- NPI Psychosis score at Weeks 2, 4, and 6
- NPI-C Hallucinations domain, Delusions domain, and Psychosis scores at Weeks 2, 4, and 6
- Quality of Life in Alzheimer's Disease (QOL-AD) score at Week 6

2.4 Safety Objectives

The safety objective for Part 1 is: To evaluate the safety and tolerability of ACP-204 60 mg and ACP-204 30 mg compared to placebo in subjects with ADP.

The safety objective for both Part 2A and Part 2B is: To evaluate the safety and tolerability of either ACP-204 60 mg or ACP-204 30 mg compared to placebo in subjects with ADP.

2.4.1 Safety Endpoints

The safety endpoints for Part 1, Part 2A, and Part 2B are:

- Treatment-emergent adverse events (TEAEs)

- 12-lead ECGs
- Vital signs, including orthostasis assessment
- Weight and body mass index (BMI)
- Physical examination results
- Clinical laboratory tests
- Global Clinician Assessment of Suicidality (GCAS) score
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Udvalg for kliniske undersøgelser (UKU) Sleepiness/Sedation and Orthostatic Dizziness scores
- Mini-Mental State Examination (MMSE) score
- Digit Symbol Substitution Test (DSST) score
- Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A) scores

2.5 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Objectives

The PK and PK/pharmacodynamic (PD) objectives are:

- To characterize the PK of ACP-204 in subjects with ADP
- To assess the PK/PD relationship of ACP-204 using efficacy and safety endpoints in subjects with ADP

2.5.1 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Endpoints

The PK and PK/PD endpoints are:

- ACP-204 PK parameters using a population PK approach
- PK/PD of ACP-204 using appropriate PK/PD analysis methods

3 STUDY DESCRIPTION

3.1 Overview of Study Design

ACP-204-006 is a master protocol for three independent, seamlessly enrolling, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2/3 studies in subjects with ADP. Subjects will be enrolled into either Part 1 (Phase 2), which will evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared with placebo in subjects with ADP, or Part 2A or Part 2B (Phase 3), which will be confirmatory of either both doses or only a single dose from Part 1.

Part 1 (Phase 2) and Part 2A and Part 2B (Phase 3) will be analyzed independently of one another.

Subjects may be enrolled into only one part of the study. No subject may be enrolled into more than one of Part 1, Part 2A, and Part 2B. Sites will begin work seamlessly on either Part 2A or Part 2B when their enrollment in Part 1 is complete. Acadia will alert each site when they can begin enrollment into Part 2A or Part 2B. Sites will be assigned in approximately equal numbers to work on either Part 2A or Part 2B, but not both. The randomization in Part 2A and Part 2B are independent, and their data are managed in two independent and separate databases. This should ensure that Part 2A and Part 2B are truly independent of each other.

Subjects who complete Part 1 or Part 2A or Part 2B (i.e., did not have an early termination [ET] from the study) will have the option of participating in the long-term OLE study, ACP-204-008, pending confirmation of eligibility.

For subjects who roll over into the OLE study (ACP-204-008), at their ACP-204-006 EOT visit, subject consent/assent and study partner/caregiver consent for ACP-204-008 must be provided per local regulations prior to the procedures being performed at the EOT visit for the present study ACP-204-006, as the EOT procedures for Study ACP-204-006 will serve as the baseline procedures for Study ACP-204-008.

Each part of the study will have the following periods, which will be applicable for individual subjects depending on whether the subject rolls over into the OLE and whether they complete the study:

- Screening Period (up to 49 days)
- Double-blind Treatment Period (6 weeks)
- Safety Follow-up Period (30 days) for Subjects Not Rolling Over into OLE (including ET subjects)
- Mortality Follow-up for ET Subjects

These periods are detailed in the sections below and diagrammed in Figure S–1 and Figure S-2.

For each separately and independently enrolling ACP-204-006 study part, the duration of participation for individual study subjects who complete the study will be up to 17 weeks, consisting of a Screening Period of up to 7 weeks, a 6-week Double-blind Treatment Period, and a Safety Follow-up Period of 30 (+4) days for those subjects who do not enroll in the OLE study (Figure S–1).

In the case of subjects who discontinue prematurely from the study, the duration of participation will also be up to 17 weeks due to the follow-up telephone call 30 (+4) days after their intended day of last dose of study drug to collect mortality data (i.e., Mortality Follow-up, Figure S-2).

In Part 1 approximately 318 subjects will be randomized in a 1:1:1 ratio to ACP-204 60 mg, ACP-204 30 mg, or placebo treatment (approximately 106 subjects per treatment group). It is

planned to randomize approximately 378 subjects in each of Part 2A and Part 2B in a 1:1:1 ratio (approximately 126 subjects per treatment group). A screen failure rate of approximately 60% is expected. Approximately 140 global sites for Part 1 and 140 global sites for Part 2A or Part 2B will participate in this study. Approximately half of the 140 sites will be assigned to work on each of Part 2A and Part 2B, and no site will work on both.

The schedule of assessments is provided in Table S–1.

An independent data and safety monitoring board (DSMB) will review safety information on a regular basis throughout the study.

The study start date is defined as the date the first subject is consented.

3.1.1 Screening Period (up to 49 Days)

During the Screening Period, if the subject has a historical positive biomarker in blood or cerebrospinal fluid, or positron emission tomography (PET) imaging, indicating amyloid plaque deposition and neuropathologic change consistent with Alzheimer's disease, then all screening procedures (including those scheduled for Visit 1a and Visit 1b) may be conducted on the same day.

If the subject does not have such historical evidence of Alzheimer's disease, then blood biomarker (BBM) positivity is required for eligibility, and Screening will be conducted across at least two visits (Visit 1a and Visit 1b). At Visit 1a, the subject will be consented and have samples collected for all laboratory tests and BBM testing to confirm Alzheimer's disease. The laboratory and BBM test results from Visit 1a will determine whether the subject can progress to Visit 1b of Screening. If there are exclusionary laboratory test results or if the BBM result is negative, the subject will be a screen failure. If the laboratory test results are not exclusionary and the BBM result is positive, the subject and caregiver will return to the clinic to complete Screening (Visit 1b). There may be circumstances in which Visit 1b will need to be performed prior to receipt of results from BBM testing. In such instances, the Investigator should consult the Medical Monitor prior to proceeding with Visit 1b.

Adult subjects aged 55 to 95 years, inclusive, will be assessed for study eligibility and prohibited medications will be discontinued if medically appropriate. Subject eligibility will be assessed by the site and the Medical Monitor through an eligibility review process as defined in the medical monitoring plan.

Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication). Subjects on prohibited medication at the beginning of the Screening Period may

discontinue that medication during the Screening Period and undergo a washout period prior to Baseline (see Appendix F and Appendix G for washout period duration).

During the Screening Period, the designated study partner/caregiver will be given instructions on engaging in a structured psychosocial interaction with the subject (brief psychosocial therapy, BPST).

Subjects who fail Screening may be rescreened for study eligibility with Medical Monitor agreement (see Section 4.3 for additional information).

3.1.2 Double-Blind Treatment Period (6 Weeks)

The Baseline visit (Visit 2) may occur up to 49 days after the first Screening visit (Visit 1a). At Visit 2, following confirmation of eligibility, including specified baseline evaluations, subjects will be randomized in a 1:1:1 ratio to 60 mg ACP-204, 30 mg ACP-204, or matching placebo, and stratified by site and by whether subjects are living in the wider community (not in an institution) or institution living (such as a nursing home).

Subjects will then take their first dose of study drug in the clinic (followed by observation in the clinic at Investigator discretion) and will be dispensed study drug to take home. It is recommended that thereafter the subject take the study drug QD at approximately the same time each day.

Assessments will be conducted at Weeks 0 (Baseline), 1, 2, 4, and 6 (EOT/ET). Every effort should be made to complete each visit in a single day.

Results at Baseline for platelets, hemoglobin, neutrophils, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine that would be exclusionary at Screening will result in ET, but enrollment of the subject will not be considered a protocol deviation (Section 4.2). Likewise, ET for any clinically significant laboratory abnormality at Baseline will not be considered a protocol deviation.

All concomitant permitted medications should remain at a stable dose throughout the study, if possible (Section 4.8.2.1). Any changes should be discussed with the Medical Monitor or designee as appropriate.

3.1.3 Safety Follow-up Period (30 Days) for Subjects Not Rolling Over into OLE

Subjects who successfully complete the 6-week Double-blind Treatment Period may be eligible to enroll in an OLE study (ACP-204-008). For subjects who discontinue prematurely from the study, two Safety Follow-up visits (telephone calls to the subject and study partner/caregiver) should be conducted, at 7 (±3) days and 30 (+4) days after the last dose of study drug, provided the subject or the subject's legally acceptable representative (LAR) has not withdrawn consent from further data collection.

3.1.4 Mortality Follow-up for ET Subjects

In addition to the safety follow-up telephone calls during the Safety Follow-up Period, for subjects who discontinue prematurely from the study and have not withdrawn consent (or had consent withdrawn by LAR) from further data collection, a telephone call to the subject and/or study partner/caregiver to confirm that the subject is still living will be conducted 30 (+4) days after the subject's intended day of last dose of study drug (i.e., the day that their last dose of study drug would have been taken had they not discontinued prematurely). If a subject has died in this follow-up period, every effort will be made to collect cause of death information where possible (including documentation; e.g., death certificate or autopsy report with subject identifiers redacted).

3.1.5 End of Study Definition

For subjects enrolling into Study ACP-204-008, a subject is considered to have completed this study if he/she has completed the EOT visit for Part 1 or Part 2A or Part 2B of this study and has not had an ET from the study.

For subjects not enrolling into Study ACP-204-008, a subject is considered to have completed this study if he/she has completed all visits, including the Safety Follow-up visit at 30 (+4) days after the last dose of study drug, for Part 1 or Part 2A or Part 2B of the study.

The primary completion date is the last date that subject data are collected for the primary outcome measure.
The study completion date is defined as the last date that subject data are collected, which includes the safety follow-up telephone calls and telephone call for mortality follow-up for subjects who have discontinued prematurely. Procedures for when a subject is lost to follow-up are provided in Section 4.6.

4 SUBJECT ELIGIBILITY, DISCONTINUATION, AND WITHDRAWAL CRITERIA

To be eligible for any part of this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria.

Some eligibility criteria involve assessments at Baseline. Subjects are not to be randomized (or dosed) until all baseline assessments for eligibility are completed and the Investigator determines that the subject is eligible taking these baseline assessment results into consideration.

4.1 Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible for participation in the study:

1. Is a male or female ≥55 and ≤95 years of age at the time of consent and living in the community or, if permitted by local regulations, in an institutionalized setting

2. Can understand the nature of the study and protocol requirements and provide written informed consent. If the subject is deemed not competent to provide informed consent, the following requirements for consent must be met:
    a. The subject's LAR (or study partner/caregiver, if local regulations allow) must provide written informed consent.
    b. The subject must provide written (if capable) informed assent per local regulations.
3. Meets clinical criteria for possible or probable AD based on the 2011 National Institute on Aging-Alzheimer Association (NIA-AA) criteria (Appendix A)
4. Has either a BBM (at Screening assessment or historical) OR documented/historical evidence such as positron emission tomography or a cerebrospinal fluid biomarker, indicating amyloid plaque deposition and neuropathologic change consistent with Alzheimer's disease as described in the 2018 NIA-AA Research Framework (Jack et al. 2018)
5. Meets the revised criteria for psychosis in major or mild neurocognitive disorder established by the International Psychogeriatrics Association (IPA) (Appendix B)
6. Has an MMSE score ≥6 and ≤24 at Screening and Visit 2 (Baseline)
7. Has sufficient verbal ability to understand and answer questions and comply with procedures, with corrective measures such as hearing aids and reading glasses if necessary, and is willing and able to participate in all scheduled evaluations and complete all required tests
8. Has had psychotic symptoms for at least 2 months prior to Screening
9. Has the following scores at Screening and Visit 2 (Baseline):
    a. NPI (subjects with an unpaid caregiver such as family or friend) or NPI-NH (subjects with a paid caregiver) Hallucinations Domain score ≥6 (Frequency×Severity) or Delusions Domain score ≥6 (Frequency×Severity) or Psychosis score (Hallucinations plus Delusions Domains scores) ≥9 AND
    b. CGI-S-ADP score ≥4
10. Lives in a stable place of residence prior to Screening, and there are no plans to change living arrangements before the end of the Safety Follow-up Period
11. Has a designated study partner/caregiver (e.g., family member, social worker, case worker or nurse) who meets the following requirements:
    a. In the Investigator's opinion, is in contact with the subject frequently enough to accurately report on the subject's symptoms and whether or not the subject is taking the study drug

b. Is fluent in the local language in which study assessments will be administered
c. Agrees to participate in study assessments and provides written consent to participate in the study

12. Can complete all study visits with a study partner/caregiver
13. Has a prior magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain (completed within past 3 years from Screening start) taken during or subsequent to the onset of dementia that is consistent with the diagnosis of AD in the Investigator's judgement. If not available, a non-contrast brain MRI or non-contrast head CT must be done during Screening.
14. If the subject is taking a cholinesterase inhibitor, memantine, or both:
    a. the dose of the medication(s) must be stable for at least 12 weeks prior to Visit 2 (Baseline) and there must be no current plan to change the dose during the course of this study; OR
    b. if the medication(s) was discontinued, the discontinuation must have occurred no fewer than 2 weeks prior to Visit 2 (Baseline).
15. If the subject is taking an antipsychotic medication at the time of Screening, the antipsychotic must be completely discontinued by 3 days prior to Visit 2 (Baseline) (i.e., no antipsychotic dose during the 3 days prior to the day of the Baseline visit) as determined by the Investigator in discussion with the Medical Monitor. Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication).
16. Must have a negative COVID-19 diagnostic test (polymerase chain reaction [PCR] rapid antigen, or transcription mediated amplification) at Screening; must not be planning to receive a COVID-19 vaccine during the study or within 30 days of the last dose of study drug.
17. If the subject is a female, she must be of nonchildbearing potential, defined as either surgically sterilized (bilateral tubal occlusion, oophorectomy, or salpingectomy; or hysterectomy) or at least 1 year postmenopausal.
18. If the subject is male and sexually active, he must use a condom (unless he is vasectomized) from the time of consent until 90 days after the last dose of study drug. If the male subject's female partner is of childbearing potential, she must use a barrier contraceptive method (e.g., condom, diaphragm) plus spermicide or a highly effective method of contraception. Highly effective methods of contraception include: combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, or

transdermal) associated with inhibition of ovulation; progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; intrauterine device (IUD); and intrauterine hormone releasing system. Male subjects must agree to not donate sperm from the time of Screening until 90 days after the last dose of study drug.

4.2 Exclusion Criteria

A subject must meet none of the following exclusion criteria to be eligible for the study:

1. Is in hospice and receiving end-of-life palliative care, or has become bedridden
2. Requires skilled nursing care (procedures that can only be administered by a registered nurse or doctor, such as but not limited to, intravenous administration of medication, procedures related to insertion or care of suprapubic catheters, and nasopharyngeal/tracheostomy aspiration)
3. Has psychotic symptoms that are primarily attributable to delirium, substance abuse, or a medical or psychiatric condition (e.g., schizophrenia, bipolar disorder, delusional disorder) other than dementia
4. Has had a major depressive episode within 3 months of Screening, according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria
5. Is actively suicidal at Screening or Visit 2 (Baseline), including an answer of "yes" to the Columbia-Suicide Severity Rating Scale (C-SSRS) questions 4 or 5 (current or over the last 6 months), or has attempted suicide in the 2 years prior to Screening
6. Has a GCAS score of 3 or 4 based on Investigator's assessment of behavior within the 3 months prior to Screening or since last visit at Visit 2 (Baseline)
7. Has evidence of a non-neurologic medical comorbidity or medication use that could substantially impair cognition
8. Has a history of ischemic or hemorrhagic stroke within the last 12 months with evidence of residual motor or sensory impairment
9. Has a known history of cerebral amyloid angiopathy, epilepsy, central nervous system (CNS) neoplasm, or unexplained syncope
10. Has atrial fibrillation unless adequately anticoagulated
11. Has symptomatic orthostatic hypotension including symptoms such as postural dizziness or pre-syncope, as measured by UKU orthostatic dizziness severity greater than zero, or history of falls associated with orthostatic hypotension, at Screening or Baseline
12. Has any of the following:
    a. greater than New York Heart Association Class II congestive heart failure (Appendix C)

b. Grade II or greater angina pectoris (by Canadian Cardiovascular Society Angina Grading Scale) (Appendix D)
c. sustained ventricular tachycardia
d. ventricular fibrillation
e. torsade de pointes
f. syncope due to an arrhythmia
g. an implantable cardiac defibrillator

13. Had a myocardial infarction within the 6 months prior to Screening
14. Has a known personal or family history or symptoms of long QT syndrome
15. Has any of the following 12-lead ECG results at Screening (triplicate ECG) or Visit 2 (Baseline, single ECG):
    a. If the subject is not on citalopram, escitalopram, or venlafaxine:
        i. QTcF >450 ms, if QRS duration <120 ms
        ii. QTcF >470 ms, if QRS duration ≥120 ms
    b. If the subject is on citalopram, escitalopram, or venlafaxine:
        i. QTcF >425 ms, if QRS duration <120 ms
        ii. QTcF >450 ms, if QRS duration ≥120 ms

    If the mean QTcF value from the set of three ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening by agreement with the Medical Monitor. In this case, the repeat set of triplicate ECGs will be used in determination of subject eligibility.
16. Has a heart rate <50 beats per minute, as measured by vital signs. If bradycardia is secondary to iatrogenic or treatable causes and these causes are addressed, a heart rate assessment can be repeated during the Screening Period.
17. Has a significant unstable medical condition that could interfere with subject's ability to complete the study or comply with study procedures
18. Has a clinically significant laboratory abnormality at Screening that, in the judgment of the Investigator or Medical Monitor, will either jeopardize the safe participation of the subject in the study or interfere with the conduct or interpretation of safety or efficacy evaluations in the study
19. Has any of the following laboratory results at Screening:
    a. Platelets ≤75,000/mm^3
    b. Hemoglobin ≤9.5 g/dL if male, or ≤8.5 g/dL if female
    c. Neutrophils, absolute ≤1000/mm^3
    d. AST >2×upper limit of normal

e. ALT >2×upper limit of normal
f. Creatinine ≥2 mg/dL
g. Hemoglobin A1c (HbA1c) ≥8.5%
h. Abnormal free thyroxine (T4)
i. Vitamin B12 deficiency
j. eGFR <30 mL/min/1.73m^2

Laboratory testing may be repeated during Screening by agreement with the Medical Monitor. The repeat results will be used in determination of subject eligibility.

20. Known history of infection with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV). Subjects with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen. Subjects with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test.
21. Has other clinically significant CNS abnormalities that are most likely contributing to the dementia or findings on MRI or CT including:
    a. intracranial mass lesion (including but not limited to meningioma [>1 cm^3 with evidence of peritumoral edema] or glioma)
    b. vascular malformation
    c. intracranial aneurysm >4 points by PHASES score (Appendix E)
    d. evidence of >4 hemosiderin deposits (definite microhemorrhage or superficial siderosis)
22. Requires treatment with a medication or other substance that is prohibited by the protocol or will be used in a way that violates a use restriction (Appendix F and Appendix G), or has been treated with anti-tau therapy or amyloid beta-directed monoclonal antibodies less than 5 half-lives prior to Screening (e.g., aducanumab within 4 months prior to Screening, lecanemab within 4 weeks prior to Screening, or donanemab within 2 months prior to Screening). Investigators should not withdraw a subject's prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication is deemed to be clinically appropriate (e.g., symptoms are not well-controlled or the subject cannot tolerate the current medication).
23. Has a BMI <18.5 kg/m^2 or known unintentional weight loss ≥7% of body weight over past 6 months
24. The urine toxicology screen result at Screening indicates the presence of amphetamine/methamphetamine, barbiturates, cocaine, ecstasy (MDMA), or phencyclidine (PCP). Subjects who test positive and have a valid prescription for amphetamines or barbiturates may be retested during Screening if they agree to abstain

from the medication for the length of their participation in the study and if abstinence from medication usage is achieved at least 7 days prior to Visit 2 (Baseline). The repeat screening test must be negative for them to participate in the study. The presence of alcohol, benzodiazepines, marijuana (THC), or opiates will not necessarily exclude the subject from the study, and eligibility will be further evaluated by the Medical Monitor on a case-by-case basis.

25. Has major surgery planned between Screening and the end of the Safety Follow-up Period
26. Has participated in or is participating in a clinical study of any investigational drug, device, or intervention, within 30 days or 5 half-lives, whichever is longer, of Visit 1a (Screening) OR has participated in a clinical study for disease-modifying therapy within 6 months of Visit 1a
27. Has previously been enrolled in any prior clinical study with ACP-204 or is currently taking ACP-204
28. Has a significant sensitivity or allergic reaction to ACP-204 or its excipients
29. Has a history of non-response to pimavanserin treatment
30. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc.
31. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason

4.3 Screen Failures

The Screening Period is described in Section 3.1.1. The Investigator should maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Screen failures are defined as subjects who consent or assent per local regulations to participate in the clinical study but are not subsequently randomized due to not meeting the criteria for participation or withdrawal of consent prior to dosing. Screen failures may be rescreened once by agreement between the Investigator and the Sponsor/Medical Monitor. Rescreened subjects should be assigned a new subject number.

In a rescreening, all screening procedures should be repeated with the exception of blood collection for BBM testing and any MRI/CT scans that may have been performed during the failed screening. The results obtained from those tests during the failed screening may be applied to the rescreening. Rescreening is not simply repeating an individual assessment that is part of the screening process. Repeating certain individual assessments that are part of screening is allowed for specific assessments as described in Section 4.2 and is not considered rescreening.

4.4 Subject Withdrawal of Consent

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time, and for any reason, without prejudice to his or her future medical care. If the subject (and/or LAR) decides to withdraw consent from all components in the study, this must be documented and no additional assessments may be performed and no additional data may be collected; in addition, no further contact with the subject will be made for the study, including access to or review of the subject's medical records. The Sponsor may retain and continue to use any data collected before such a withdrawal of consent. The subject or LAR may request destruction of any samples taken and not tested, prior to their withdrawal of consent, and the Investigator must document this in the site study records.

4.5 Subject Discontinuation from Study Drug and Study

Subjects may be discontinued from the study drug or the study for a number of reasons, including, but not limited to, those listed below.

- Adverse event (AE)
- Lack of efficacy
- Lost to follow-up (Section 4.6)
- Non-compliance with study drug (Section 5.1.6)
- Protocol deviation
- Use of prohibited medication (Section 4.8.2.1)
- Other (e.g., loss of LAR/caregiver/study partner without replacement, unacceptable lab results at Baseline, site terminated by Sponsor)

Subjects **must** be discontinued from the study drug or the study for a number of reasons, including, but not limited to, those listed below.

- Death
- Physician decision
- Pregnancy (Section 7.4.3)
- Study terminated by Sponsor (Section 4.7)
- Withdrawal of consent by subject (or by LAR)
  - When the subject (and/or LAR) decides to withdraw consent from all components in the study, this must be documented, and no additional assessments may be performed, and no additional data may be collected (Section 4.4)
- Withdrawal by subject (or by LAR)

- When the subject (and/or LAR) wants to discontinue treatment with the study drug and agrees to the evaluations specified at the EOT/ET visit and/or at Safety Follow-up and/or at Mortality Follow-up (whichever is applicable), as outlined in Table S–1, the agreed assessments should be conducted. This is not considered a withdrawal of informed consent.
- In any case, the subject's reason for wanting to discontinue treatment (if provided) and the decision whether to agree with the applicable assessments for study termination must be documented (in the source documentation).

Note that loss of LAR/caregiver/study partner will result in discontinuation only if the LAR/caregiver/study partner is not replaced. Any change of LAR/caregiver/study partner must be approved by the Medical Monitor and documented in the electronic case report form (eCRF). Any new LAR/caregiver/study partner must meet the relevant inclusion criteria.

4.5.1 Handling of Subject Discontinuation During the Treatment Period

Unless the subject or LAR has withdrawn consent from all components of the study (Section 4.4), every reasonable effort should be made to complete Visit 6 (EOT/ET) and the Safety Follow-up visits and Mortality Follow-up (as outlined in Table S–1) if a subject discontinues treatment prematurely during the treatment period of the study. All available information will be reported on the applicable pages of the eCRF.

If a subject is discontinued from treatment because of an AE, every reasonable attempt should be made to follow and appropriately treat (or refer for treatment) the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable. For subjects who continue to be followed for safety, serious adverse events (SAEs) should continue to be reported as described in Section 7.4.2. All SAEs will continue to be followed and appropriately treated until such events have resolved or the Investigator deems them to be chronic or stable.

4.6 Subject Lost to Follow-up

A subject will be considered lost to follow-up if they fail to attend a scheduled visit (including the Safety Follow-up visit at 30 [+4] days after the last dose of study drug or Mortality Follow-up if applicable) and the study subject or caregiver/study partner is unable to be contacted by the study site **after repeated documented attempts**.

Every reasonable effort should be made to contact the subject and caregiver/study partner and will include a minimum of three documented phone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods. All contact attempts are to be documented in the source documents.

4.7 Study Discontinuation

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs
- Medical, ethical, or business reasons affecting the continued performance of the study

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the DSMB, the independent ethics committees (ECs)/institutional review boards (IRBs), the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Regulatory authorities also have the right to terminate the conduct of the study in their region for any reason.

4.8 Prior and Concomitant Therapy

All medications used from Screening until completion of the Safety Follow-up Period are to be recorded. Also, medication history will be obtained at Screening.

4.8.1 Prior Medication

Prior medication is defined as any medication with a stop date prior to the date of the first dose of study drug. Lifetime antipsychotic use and response, as well as all other medications used up to 24 weeks prior to Baseline, are to be recorded.

4.8.2 Concomitant Medication

Concomitant medication is defined as any medication that is ongoing at the first dose of study drug or with a start date between the dates of the first dose and last dose of study drug, inclusive.

Medication taken after the date of the last dose of study drug is considered post-treatment medication.

In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication without prior consultation with the Investigator (unless the subject is receiving treatment for a medical emergency).

The Investigator may prescribe appropriate medication to treat AEs (see Appendix F and Appendix G).

4.8.2.1 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between Screening and the end of Visit 6 (EOT/ET) as specified in Appendix F and Appendix G. These appendices do not constitute an exhaustive list, and any questions regarding prohibited and restricted medications should be discussed with the Medical Monitor or designee. The Investigator may prescribe appropriate medication to treat AEs.

For subjects who roll over into the OLE study (ACP-204-008), prohibitions and restrictions for concomitant medications will begin at their ACP-204-006 EOT visit when subject consent/assent for ACP-204-008 is provided.

Medications that can prolong QT interval are prohibited (or restricted) as specified in Appendix F.

Permitted concomitant medications should remain at a stable dose throughout the study; however, the dose of medications used to treat AEs may be adjusted according to Investigator judgment.

If a subject is on a medication restricted by the protocol, the medication should be adjusted if it is determined by the Investigator to be clinically appropriate (e.g., if the subject's symptoms are not well-controlled or if the subject cannot tolerate the current medication) in consultation with the treating physician.

Subjects who require current treatment with a prohibited medication will be discontinued from the study.

Subjects who have taken a prohibited medication (as per Appendix F and Appendix G) will be discontinued from the study unless:

- the prohibited medication has been discontinued, AND
- discontinuation from the study presents an unacceptable medical risk to the subject

The justification to allow the subject who has taken a prohibited medication to continue in the study will be made by the Sponsor/Medical Monitor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the study, this will be reported as a major protocol deviation and not a waiver.

4.8.3 Rescue Medications, Treatments, and Procedures

Benzodiazepines are allowed as rescue medication as needed for severe neuropsychiatric or behavioral disturbances. Benzodiazepine rescue medication, lorazepam up to 1 mg/day or equivalent, may be prescribed to the subject by the Investigator. In case of uncertainty, the Investigator may consult with the Medical Monitor to determine an equivalent dose. Reasonable

efforts should be made to use the minimum dose necessary for symptom management. The following rescue medications may be used:

- alprazolam
- clonazepam
- lorazepam
- oxazepam
- temazepam
- midazolam
- triazolam

Long-acting benzodiazepines must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit and are prohibited through the end of Visit 6 (EOT/ET) (Appendix F). Rescue medication may not be used within 12 hours prior to a visit where there is an efficacy assessment. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

4.9 Lifestyle Considerations

Participation in this study does not entail any significant lifestyle restrictions.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply ACP-204 30 mg and 60 mg capsules and matching placebo capsules. The ACP-204 30 mg, 60 mg, and placebo capsules are identical in size and appearance.

The drug substance, ACP-204 tartrate hydrate, is a crystalline, white to off-white powder. ACP-204 tartrate hydrate is freely soluble in water.

ACP-204 capsules consist of a white opaque body and white opaque cap, and contain ACP-204 tartrate hydrate, microcrystalline cellulose, and magnesium stearate. ACP-204 30 mg and 60 mg capsules contain ACP-204 tartrate hydrate in amounts that deliver 30 mg and 60 mg of active free base, respectively. ACP-204 capsules are immediate release and intended for oral administration.

Placebo capsules also consist of a white opaque body and white opaque cap, and contain only microcrystalline cellulose.

The ACP-204 and placebo capsule shells are composed of hypromellose (hydroxypropyl methylcellulose) and titanium dioxide.

ACP-204 capsules and placebo capsules are manufactured under current Good Manufacturing Practice.

ACP-204 capsules and placebo capsules will be provided in either a high-density polyethylene bottle containing 20 capsules or in ACLAR® blisters (10 capsules per blister card). Each type of packaging will be labeled as required per country requirement.

During the treatment period, study drug will be distributed in a quantity sufficient to ensure the subject has an adequate supply of study drug between study visits.

5.1.2 Storage

ACP-204 capsules should be stored in a secure area with restricted access at controlled room temperature. Please see Pharmacy Manual for more detail.

5.1.3 Dosing and Administration

The first dose of study drug will be administered at the clinic. Study drug will be dispensed to the subject to take home at the Baseline visit and later visits indicated in Table S–1. Each daily dose consists of one capsule of study drug. Subjects should be instructed to take one capsule, orally, QD. It is recommended that the subject take the study drug at approximately the same time each day. The study drug capsules may be taken with or without food.

Sufficient study drug will be provided for the last dose of study drug to be taken on the day of Visit 6 (EOT/ET), where needed.

5.1.4 Method of Assigning Subjects to Treatment Groups

At Week 0 (Visit 2), eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1:1 ratio to receive either ACP-204 60 mg, ACP-204 30 mg, or placebo. All subjects will be centrally assigned to randomized study drug using an IRT. Before the study is initiated, the log in information and directions for the IRT system will be provided to each site.

The randomization will be stratified by site and by whether subjects are living in the wider community (not in an institution) or institution living (such as a nursing home). The assignments will be based on a pre-generated permuted-block randomization schedule.

5.1.5 Blinding

Treatment assignments will be blinded to all study subjects, study partners/caregivers, Investigators, raters, site personnel, and Sponsor personnel. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or designee to the treatment codes, and providing identical capsules and packaging for the study drug and placebo treatments. Data will be unblinded for Part 1 after Part 1 database lock and for Part 2A and Part 2B after their respective database locks, unless specified otherwise.

In the event of a medical emergency where breaking the blind is required so that appropriate medical care can be provided, treatment assignments for the affected subject may be unblinded to the Investigator through the IRT system. The date and rationale for unblinding must be clearly explained in source documentation. The Investigator is responsible for all study-related medical decisions and may immediately unblind study drug without prior contact with the Sponsor in an emergency as assessed clinically by the Investigator. The Investigator should consider with emergency unblinding how critical that information is for ongoing management of patient safety. The Investigator should contact the Sponsor/Medical Monitor promptly regarding any emergency unblinding. Once a subject's treatment assignment is disclosed to the Investigator, the subject should have study drug discontinued.

In the event of a potential suspected unexpected serious adverse reaction (SUSAR), in accordance with current health authority guidance, treatment assignments for the affected subject may be unblinded to a controlled group of the Sponsor's Safety and/or Regulatory personnel for reporting purposes.

If pregnancy occurs during the study, the pregnant subject should be discontinued from the study and unblinded so that counseling may be offered based on whether the fetus was exposed to the active study drug or placebo. See also Section 7.4.3.

See Section 9.12 for blinding/unblinding in relation to DSMB review.

5.1.6 Study Drug Compliance

The Investigator or designated study center personnel will maintain a log of all study drug dispensed and returned during the study. Study drug supplies for each subject will be inventoried and accounted for throughout the study to verify the subject's compliance with the dosage regimen. Subjects will be counseled regarding compliance at every visit. Subjects who have <80% or >120% compliance may be discontinued from the study. If a subject shows significant undercompliance (<80%) between any two scheduled visits, the Medical Monitor should be notified to determine if the subject remains eligible for the study or shall be discontinued from the study and whether the incident should be considered a protocol deviation.

If a subject misses one dose of study drug, he or she should not take an extra dose the next day.

5.1.7 Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported using the Sponsor's Overdose Reporting Form, irrespective of outcome, even if toxic effects were not observed (Section 7.4.4). All events of overdose are to be captured as protocol deviations.

Sponsor does not recommend specific treatment for an overdose.

5.2 Investigational Product Accountability Procedures

The Investigator or designee will keep current and accurate records of the study drug dispensed, used, and returned for each subject to assure the regulatory authority and the Sponsor that the study drug is being handled appropriately. Subjects will be instructed to return all packaging and unused study drug to the Investigator at regularly scheduled study visits and ET visits. Any study drug supplied is for use in this study only and should not be used for any other purpose.

At appropriate intervals during the study, study drug reconciliation will be performed by the Sponsor (or designee) who may return appropriate unused study drug and used and unused packaging to the Sponsor's designee for destruction.

At the conclusion of the study, final study drug reconciliation will be conducted at the site. Final study drug accountability documentation will be maintained at both the site and at the Sponsor. Any remaining unused study drug and all used and unused packaging will be sent back to the Sponsor's designee for destruction, as allowed by country-specific regulations. Documentation of study drug destruction will be recorded and maintained by both the Sponsor and the Sponsor's designee.

6 STUDY ASSESSMENTS

Study-specific assessments are detailed below. All assessments will be completed according to the schedule described in Table S–1. Every effort should be made to complete the required procedures and evaluations at the designated visits and times.

6.1 Screening Assessments

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator should maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

In addition to the screening assessments/procedures listed in this section, some assessments related to efficacy and safety (Section 6.2 and Section 6.3, respectively) must also be performed for eligibility evaluation (see Section 4.1, Section 4.2, and Table S–1).

6.1.1 Medical, Psychiatric, Dementia, and Neurological Histories; Clinical Validation Inventory for Study Admission; and Demographics

A complete medical history will be obtained from each potential subject, including details of the subject's psychiatric history and treatment (including prior use of and response to antipsychotic medication), details of the subject's dementia diagnosis and treatment (including date of onset of cognitive impairment), and details of any neurologic diagnosis and treatment.

Subjects may be asked to provide pharmacy or medical records to substantiate the medication history (Section 4.8.1).

Pre-existing medical conditions should be captured as medical history. Any new medical condition or worsening of a pre-existing medical condition after the informed consent form (ICF) has been signed will be captured as an AE.

The Clinical Validation Inventory for Study Admission (C-VISA™) is a customized screening assessment tool that details the required elements for subject eligibility, enabling site-independent confirmation of sufficient documentation to support subject selection. Once completed, the C-VISA™ is submitted for review by Signant Health to confirm that protocol eligibility criteria pertaining to diagnostic eligibility, psychiatric history, and psychiatric assessments are met.

Demographic information, including date of birth, sex, and race and ethnicity as reported by the subject, will be recorded as well (as allowed by local regulations).

6.1.2 Brain Imaging (MRI/CT)

A non-contrast brain MRI or non-contrast head CT will be completed if the subject has not had an MRI or CT scan completed (a) within the past 3 years AND (b) during or subsequent to the onset of dementia. If the Investigator believes a brain MRI with contrast or a head CT with contrast is clinically warranted, such a study may be done. The purpose of the scan is to evaluate criteria excluding a clinically significant CNS abnormality (Section 4.1).

6.1.3 Brief Psychosocial Therapy

During the Screening Period, the designated study partner/caregiver will receive instruction for engaging in a structured psychosocial interaction with the subject. This psychological intervention is intended to aid the subject and caregiver in managing the subject's neuropsychiatric symptoms. Study partners/caregivers will be instructed on the BPST by trained site personnel and will have approximately weekly supportive telephone contacts during Screening. It is recommended that the study partner/caregiver conduct the intervention with the subject at a frequency of 5 times per week (where possible to achieve a minimum of 3 times per week) for the duration of the Screening Period.

6.1.4 Biomarkers for Alzheimer's Disease for Eligibility

At Screening, blood will be collected (Visit 1a) and analyzed for biomarkers for Alzheimer's disease that will be required for eligibility if the subject has no documented historical evidence indicating amyloid plaque deposition and neuropathologic change consistent with Alzheimer's disease. Subjects who are confirmed to have a BBM consistent with Alzheimer's disease and indicating amyloid plaque deposition and neuropathologic change based upon these assessments

as described in the 2018 NIA-AA Research Framework (Jack et al. 2018) will be eligible for inclusion into the study.

A blood sample for testing additional biomarkers will be collected at Baseline (Section 6.5).

6.2 Efficacy Assessments

This section describes efficacy assessments, among which are SAPS, NPI and CGI assessments. In cases where a site is unable to provide an appropriate rater to conduct these assessments, a remote blinded rater (i.e., mental health evaluator) from a centralized service will conduct them in real-time using audio-conference technology.

6.2.1 Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions

The SAPS (Andreasen 1984) was designed to measure positive psychotic symptoms. Positive symptoms include hallucinations, delusions, abnormalities in language and behavior, and disordered thought processes. The SAPS-H+D will be administered in this study. The Hallucinations and Delusions subscales consist of 20 items, including global ratings of severity both of hallucinations (H7) and of delusions (D13), respectively. The SAPS-H+D total score is the sum of the scores of the Hallucinations and Delusions subscales. The hallucinations domain score (SAPS-H) is the sum of the 7 hallucinations item scores, and the delusions domain score (SAPS-D) is the sum of the 13 delusions item scores.

Every effort should be made to complete the Clinical Global Impression–Severity (CGI-S)/Clinical Global Impression–Improvement (CGI-I) and the SAPS-H+D in a single day at all applicable visits. In the event of a split visit, completion of the CGI-S/CGI-I and the SAPS-H+D on the same day should be prioritized.

6.2.2 Clinical Global Impression–Severity–ADP and Clinical Global Impression–Improvement–ADP Scales

The CGI-S-ADP scale is the CGI-S scale applied in the ADP context, in which hallucinations and delusions are the symptoms of interest. Likewise, the CGI-I-ADP scale is the CGI-I scale applied in the ADP context, in which hallucinations and delusions are the symptoms of interest.

The CGI-S scale is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's symptoms at the time of assessment using the Investigator's judgment and past experience with subjects who have the same disorder (e.g., ADP) (Guy 1976).

The CGI-I scale is a clinician-rated, 7-point scale that will be used to rate the improvement in the subject's symptoms at the time of assessment, relative to the symptoms at Baseline.

Every effort should be made to complete the CGI-S/CGI-I and the SAPS-H+D in a single day at all applicable visits. In the event of a split visit, completion of the CGI-S/CGI-I and the SAPS-H+D on the same day should be prioritized.

6.2.3 Sleep Disorders Inventory

The SDI is an expanded version of one item of the NPI (Tractenberg et al. 2003). It consists of the seven subquestions from the NPI sleep disturbance item. Each of the subquestions was made into a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the patient-participant for the 2 weeks prior to the visit. Thus, in contrast to a single rating for frequency and severity for all sleep disturbance-related behaviors, which would be incorporated into an overall NPI score, the SDI score is derived after the caregiver rates the frequency and severity of each of the seven separate sleep disturbance symptoms. Caregiver distress ratings are not part of the SDI score, but distress is measured. The SDI score is calculated as the average of seven frequency ratings×average of seven severity ratings, with a range of 0 through 12.

6.2.4 Quality of Life in Alzheimer's Disease

The QOL-AD instrument is a brief, 13-item measure designed specifically to obtain a rating of the patient's QOL from both the patient and the caregiver (Logsdon et al. 1999; Logsdon et al. 2002). It was developed for individuals with dementia. It includes assessments of the individual's physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores around the house, ability to do things for fun, money, and life as a whole. Caregivers complete the measure as a questionnaire about their patients' QOL, while patients complete it in interview format about their own QOL. Each item is rated on a 4-point scale. The score is the sum of all item ratings. Patient and caregiver reports can be evaluated separately and/or combined into a single score.

6.2.5 Neuropsychiatric Inventory

The NPI was developed to assess psychopathology in dementia patients (Cummings et al. 1994). The original NPI evaluated 10 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behavior. Two other domains, nighttime behavior disturbances and appetite and eating abnormalities, were subsequently added to the NPI (Cummings 1997). The score of each item (i.e., domain), if present, represents the product of symptom frequency (4-point scale) and severity (3-point scale). The NPI total score is the sum of the scores of the 10 neuropsychiatric domains (excluding nighttime behavior disturbances and appetite and eating abnormalities).

Additionally, a caregiver distress rating (or NPI-D, Kaufer et al. 1998) will be determined for the 12 individual domains (6-point scale), and the sum of the caregiver distress ratings for the

10 neuropsychiatric domains (excluding nighttime behavior disturbances and appetite and eating abnormalities) will be reported as the NPI Caregiver Distress total score.

The NPI will be used for subjects with an unpaid caregiver such as family or friend.

6.2.6 Neuropsychiatric Inventory – Nursing Home Version

The NPI-NH (Cummings et al. 1994; Wood et al. 2000) was developed to assess psychopathology in patients with dementia in nursing homes and evaluates 12 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities. The nursing home version of this scale was designed to examine psychopathology in nursing home patients and has been validated for use in this population (Wood et al. 2000). The score of each item (i.e., domain), if present, represents the product of symptom frequency (4-point scale) and severity (3-point scale). The NPI-NH total score is the sum of the scores of the 10 neuropsychiatric domains (excluding nighttime behavior disturbances and appetite and eating abnormalities).

Additionally, a caregiver occupational disruptiveness rating will be determined for the 12 individual domains (6-point scale), and the sum of the occupational disruptiveness ratings for the 10 neuropsychiatric domains (excluding nighttime behavior disturbances and appetite and eating abnormalities) will be reported as the NPI Occupational Disruptiveness total score.

The NPI-NH will be used for subjects with a paid caregiver.

6.2.7 Neuropsychiatric Inventory Psychosis

The NPI Psychosis score is the sum of domain A (delusions) and domain B (hallucinations) scores (each a product of symptom frequency and severity) of either the NPI or NPI-NH, as appropriate for a given subject.

6.2.8 Neuropsychiatric Inventory – Clinician

The NPI-C (de Medeiros et al. 2010) is a revised version of the NPI (Cummings et al. 1994) that includes expanded domains and items, and a clinician-rating methodology. With the NPI-C, data are acquired directly from patients, unlike the NPI where data are acquired only from informants.

There are two important rating changes in the NPI-C. The first is item-by-item scoring. In the NPI, a knowledgeable informant provides a global domain rating for frequency, severity, and level of caregiver distress related to the group of items within a given domain. The domain score is the product of the ratings for domain frequency and severity. In the NPI-C, ratings for frequency (0 [never] to 4 [very frequently]), severity (0 [none] to 3 [marked]) and distress (0 [not distressing] to 5 [extremely distressing]) are provided for each item and summed to create a total domain score for each of these parameters.

In the clinician rating approach, the knowledgeable informant is first asked to provide frequency, severity, and distress ratings for items as described above. Separately, the rater also interviews the patient. Even if the patient lacks the ability or insight to describe experiences of neuropsychiatric symptoms accurately, the interview gives the clinician rater an opportunity to compare the knowledgeable informant's insights to the patient's perceptions.

To rate various item responses, the clinician can ask for additional details during either interview and may consult other sources of information such as the patient's chart or other caregivers familiar with the case in order to provide an overall severity rating for a given domain item.

The final NPI-C has 14 domains and a total of 142 items. The domains are delusions, hallucinations, agitation, aggression, dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor disturbance, sleep disorders, appetite and eating disorders, and aberrant vocalizations.

Based upon informant ratings of individual symptom domain items including frequency, severity, and distress, along with frequency reported by patients, an overall clinical impression of severity is made by the rater for each domain symptom item and a total is provided based upon this severity score for each domain. For this study, only the domains of delusions (domain A) and hallucinations (domain B) will be assessed. The sum of the delusions and hallucinations clinical impression of severity is the NPI-C Psychosis score in this study.

The NPI-C assessment is incorporated into the study protocol as part of Amendment 3. However, it is acknowledged that the timing of availability of the NPI-C assessment may vary across different regions and clinical sites. Therefore, the administration of the NPI-C will commence when the necessary materials and resources become available/approved at each respective site. Until that time, the assessment is not required, but once available, sites should commence administration with subjects at their Screening visit. The NPI-C should not be first implemented with any subject at their Baseline visit or later.

6.3 Safety Assessments

6.3.1 Physical and Neurological Examination

A general physical examination will be conducted. The physical exam procedures will include the following organ systems:

- Head, ears, eyes, nose, and throat
- Skin
- Cardiovascular
- Respiratory
- Abdomen

- Genitourinary (optional)
- Musculoskeletal
- Lymph nodes

In addition, a neurological exam (cranial nerves, motor, sensory, reflexes, gait, and coordination) will be conducted.

6.3.2 Vital Signs

Vital signs will include body temperature, resting respiration rate, and orthostatic (supine and standing) blood pressure (BP, systolic and diastolic) and pulse rate.

The following procedures for orthostatic BP and pulse rate evaluation should be followed each time vital signs are measured. After the subject has been supine for approximately 5 minutes, BP and pulse rate will be measured and recorded, and the subject will then be instructed to rise to a standing position if able. Blood pressure and pulse rate will again be measured and recorded approximately 1 minute and 3 minutes (no later than 5 minutes) after standing. Subjects unable to stand may be assessed while sitting upright. The same position and arm should be used each time vital signs are measured for a given subject.

Orthostatic hypotension is defined as a decrease in systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg after transitioning from the supine position to standing (or sitting upright if unable to stand) after 1 or 3 minutes.

6.3.3 Peripheral Edema

The possible presence of peripheral edema will be assessed at the study visits indicated in Table S–1. Peripheral edema present at Screening should be listed as medical history. New or worsening peripheral edema after Screening should be reported as an AE with stop/start dates noted, severity rated, relation to study drug, treatment, and outcome described, as for other types of AE. Clinicians should determine if any peripheral edema is pitting or non-pitting, arm or leg, unilateral or bilateral, acute or chronic, as well as its likely cause and treatment.

6.3.4 Height, Weight, and Body Mass Index

Height will be measured and reported.

Weight will be measured and reported.

Body mass index (BMI) will be calculated based on height at Screening and current weight measurements using the following formula: $Weight\ (kg)/[height\ (m)]^2$.

6.3.5 Electrocardiograms

All 12-lead ECGs will be complete, standardized recordings.

Electrocardiograms should be performed before blood sampling or at least 30 minutes after blood sampling. The subject should rest in a supine position for 5 minutes before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician at the research site. All ECGs will also be centrally read; the interpretation by the central cardiologist is considered the official interpretation. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF, and QTcB intervals) will be included and summarized in the subject's study records.

The ECG will be completed in triplicate at Screening and as a single tracing at all other visits. The following conditions apply:

- If the mean QTcF value from the set of ECGs done at Screening is prolonged due to an identifiable cause, and it is medically appropriate to address that cause, a repeat set of triplicate ECGs may be performed during Screening by agreement with the Medical Monitor. In this case, the repeat set of triplicate ECGs will be used in determination of subject eligibility.
- At Baseline, a subject may be enrolled based on the review and interpretation of ECG results by a qualified clinician at the research site. If the interpretation of the ECG by the central cardiologist indicates QTcF outside of the allowable range, the subject will be discontinued from the study, but enrollment of the subject will not be considered a protocol deviation.
- If a site performs in a single session more than the three ECGs prescribed at Screening or the single ECG prescribed at Baseline, the mean QTcF/QRS values of all the tracings of adequate quality will be used to determine eligibility.
- For all prescribed ECG assessments, repeats of ECGs performed because of abnormalities due to an identifiable cause are considered to be part of a separate ECG session. Repeat ECG values will not be averaged with values from another ECG session. All ECG values will be included in the subject's study records.

6.3.6 Laboratory Evaluations

Clinical laboratory sample collection is encouraged, but not required to be completed under fasting conditions. The laboratory evaluations will include, but are not limited to, the following:

Clinical chemistry serum tests (CHEM)

- Sodium, potassium, bicarbonate, chloride, phosphate, calcium, blood urea nitrogen (BUN), creatinine (CR), uric acid
  - The eGFR will only be calculated from CR at Screening.
- Magnesium

  - Magnesium should only be performed at Screening.
- Glucose
- Albumin (ALB)
- Total protein
- ALT, AST, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
- Lipid panel
  - Total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol, cholesterol/HDL ratio, non-HDL cholesterol
- HbA1c should only be performed at Screening and Visit 6 (EOT/ET).
- Creatine kinase (CK)/creatine phosphokinase (CPK)
- Vitamin B12
  - Vitamin B12 should only be performed at Screening.

Endocrinology tests (ENDO)

- Thyroid function tests
  - Thyroid-stimulating hormone (TSH) and free T4
    - TSH should be performed only at Screening.
    - Free T4 will be measured only if the TSH is abnormal.
- Prolactin

Hematology tests

- Complete blood count (CBC) including:
  - White blood cell (WBC) count
  - Complete differential (relative and absolute, including absolute neutrophil count)
  - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
  - Reticulocyte count

COVID-19 tests

- A COVID-19 test (PCR, rapid antigen, or transcription mediated amplification) will be performed at Screening.

Urinalysis (UA)

- Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, nitrate/nitrite, leukocyte esterase, microscopic analysis.

- Reasonable efforts should be made to collect a urine sample from all subjects, and this is mandatory when the test is required for eligibility. After enrollment, where collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent), failure to collect a urine sample should be recorded in the subject's eCRF, and will not be considered a protocol deviation.

Urine toxicology screen

- Urine toxicology screen will test for controlled substances and alcohol (i.e., ethanol). The following controlled substances may be tested with a urine toxicology screen according to the schedule presented in Table 6–1: amphetamine, methamphetamine, barbiturates, cocaine, ecstasy (MDMA), phencyclidine (PCP), benzodiazepines, marijuana (THC), methadone, morphine/opiates. With certain exceptions described below, positive results will make a subject ineligible or result in ET.
- In the event of a positive result for a particular controlled substance or alcohol at any visit, a reflex test with the same sample will be performed to rule out a false positive. If this reflex test result for the same controlled substance or alcohol is negative, then the subject will not be ineligible or discontinued based on the prior positive result.
- The eligibility consequences of positive test results for amphetamines, barbiturates, alcohol, benzodiazepines, marijuana (THC), and opiates are described in Section 4.2.
- For continued participation in the study, positive test results for alcohol, benzodiazepines, marijuana (THC), or opiates will not necessarily result in ET. These will be evaluated by the Medical Monitor on a case-by-case basis. See Appendix F for prohibited benzodiazepines and opiates.
- Reasonable efforts should be made to collect a urine sample from all subjects; however, if after Screening collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent), controlled substances (including the opiate buprenorphine) and alcohol will be tested from a blood sample where local regulations permit this. Where testing from a blood sample cannot be performed, this will not be considered a protocol deviation for testing after enrollment. However, for eligibility, testing for controlled substances and alcohol in urine (not blood) must be performed.
- A urine toxicology screen should be performed as close as possible to the time of any seizure activity.

Blood alcohol test

- Blood alcohol test should be performed as close as possible to the time of any seizure activity.

Laboratory evaluations will be completed according to the schedule presented in Table 6–1 and procedures detailed in the study laboratory manual. Additional safety testing may be performed at the discretion of the Investigator or designee.

Table 6–1 Safety Laboratory Evaluations

Visit	Tests
Screening	CHEM, ENDO, CBC, COVID-19 test, UA, urine toxicology screen
Visit 2 (Baseline)	CHEM, ENDO, CBC, UA, urine toxicology screen
Visit 4 (Week 2)	CHEM, ENDO, CBC, UA
Visit 6 (Week 6, EOT/ET)	CHEM, ENDO, CBC, UA, urine toxicology screen

Abbreviations: CBC=complete blood count; CHEM=clinical chemistry serum tests; ENDO=endocrinology tests; COVID-19=coronavirus disease 2019; EOT=end of treatment; ET=early termination; UA=urinalysis

6.3.7 Global Clinician Assessment of Suicidality

The GCAS is a clinician-rated, 5-point scale that is designed to rate the subject's suicidality based on the report of the subject, the report of the study partner/caregiver, and the clinician's global assessment. Ratings can be 0 ("Absent"), 1 ("Feels life is not worth living"), 2 ("Wishes he/she were dead or any thoughts of possible death to self"), 3 ("Suicidal ideas or gesture"), or 4 ("Attempt at suicide"). The Investigator will record a subject rating, a study partner/caregiver rating, and a clinician rating.

At Screening lifetime suicidality and suicidality for the past 3 months will be assessed, and at all other designated visits, suicidality since the previous visit will be assessed.

If at any time the GCAS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject (Section 4.5) and implement appropriate treatment.

The GCAS allows for capture of reports of suicidal behavior in the patient by the study partner or caregiver in subjects with dementia who may not be able to give reliable information.

6.3.8 Columbia–Suicide Severity Rating Scale

The C-SSRS monitors changes in suicidal thinking and behavior over time, in order to determine risk (Posner et al. 2011). The following four constructs are measured: the severity of ideation, the intensity of ideation, behavior, and lethality.

The C-SSRS will be used to assess suicidal ideations and behaviors, and assessment will be based upon both subject and caregiver informant report. The C-SSRS allows for mapping to Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories.

The Baseline/Screening version will be administered at Screening, and the "Since Last Visit" version will be administered at all other designated visits. The C-SSRS results for each subject should be reviewed by the Investigator at each visit. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 4.5).

6.3.9 Udvalg for Kliniske Undersøgelser Sleepiness/Sedation and Orthostatic Dizziness

The Committee on Clinical Investigations of the Scandinavian Society of Psychopharmacology, Udvalg for kliniske undersøgelser or UKU, developed a comprehensive rating scale for adverse effects in drug trials (Lingjærde et al. 1987). The complete scale includes 48 symptom items. Each of these are rated on a 4-point scale: 0=not or doubtfully present, 1=present to a mild degree, 2=present to a moderate degree, or 3=present to a severe degree; and scoring should be done without regard to possible connection with drug. Scoring is based upon all relevant information available including patient reports from self and others, and physician observations. Most symptoms are assessed in the "here and now" or cross-sectionally, but where appropriate are rated based upon severity within the last 3 days, and for some this retrospective assessment may be longer such as when considering weight changes. The physician's clinical assessment is given priority over the patient report. Following assessment of severity, symptoms are classified according to connection with study drug as "improbable," "possible," or "probable." Finally, a last evaluation is made as to whether symptoms should be reported to an agency. A total side effect evaluation for all 48 symptoms can be made with a global evaluation of impact on functioning.

For this study, only the severity rating and connection to study drug of the Sleepiness/Sedation and Orthostatic Dizziness items of the UKU rating scale will be done.

Sleepiness/Sedation: Diminished ability to stay awake during the day. The assessment is based on clinical signs during the interview. The possible severity ratings for Sleepiness/Sedation are:

0: No or doubtful sleepiness

1: Slightly sleepy/drowsy as regards facial expression and speech

2: More markedly sleepy/drowsy. The patient yawns and tends to fall asleep when there is a pause in the conversation.

3: Difficult to keep the patient awake and to wake the patient, respectively

Orthostatic Dizziness: Feeling of weakness, everything going black, buzzing in the ears, increasing tendency to faint when changing from supine or sitting position to upright position. The possible ratings for Orthostatic Dizziness are:

0: No or doubtful

1: Clearly present, but requires no special countermeasures

2: Hampering, but can be neutralized by slow and/or stagewise change to upright position

3: Threatening fainting or real episodes of fainting despite careful change of position, with a tendency to this type of dizziness as long as the patient is in an upright position

Any increase in the severity rating of Sleepiness/Sedation or Orthostatic Dizziness from the baseline score at subsequent visits will be reported as an AE (see Section 7.1.1 for definition of an AE).

6.3.10 Mini-Mental State Examination

The MMSE is a brief 30-point questionnaire that is used to quantitatively assess cognition (Folstein et al. 1975). The MMSE includes simple questions and problems in a number of areas: the time and place of testing, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. The MMSE is being used in this study to evaluate/screen for cognitive impairment and as a safety measure.

6.3.11 Digit Symbol Substitution Test

The Digit Symbol Substitution Test (DSST) evaluates attention and psychomotor speed. Jaeger (2018) notes that the DSST is sensitive to change in cognitive function across a wide range of clinical populations. The DSST has been useful to demonstrate the effects of drugs on cognition. Jaeger notes further that the DSST has been a standard tool in clinical pharmacology and is sensitive to impairments and improvement in processing speed, executive functioning, and working memory. Performance on the DSST correlates with real-world functional outcome. The DSST is a paper-and-pencil cognitive test presented on a single sheet of paper that requires a subject to match symbols to numbers according to a key located on the top of the page. The subject copies the symbol into spaces below a row of numbers. The number of correct symbols within the allowed time, usually 90 to 120 seconds, constitutes the score. The DSST contained in the Wechsler Adult Intelligence Scale or WAIS is called 'Digit Symbol' in WAIS-Revised, 'Digit Symbol Coding' in WAIS-III, and 'Coding' in WAIS-IV. In this study the WAIS-IV Coding will be used.

6.3.12 Extrapyramidal Symptom Rating Scale–Abbreviated

The ESRS (Chouinard and Margolese 2005) was developed to assess drug-induced movement disorders such as Parkinsonism, akathisia, dystonia and tardive dyskinesia with established

reliability, validity, and sensitivity. It has demonstrated excellent inter-rater reliability in idiopathic Parkinson's disease (Chouinard et al. 1984). It consists of a questionnaire of Parkinsonian symptoms, physician examination of Parkinsonism, dyskinetic movements and global impression of tardive dyskinesia. The ESRS-A, an accepted modified form of the original ESRS, will be used during study drug treatment to monitor for any worsening in extrapyramidal symptoms or signs at scheduled visits.

6.3.13 Adverse Event Assessments

Adverse events will be assessed as per Table S–1 and Section 7.

6.4 Pharmacokinetic Assessments

As indicated in Table S–1, one PK sample will be collected at each of Weeks 0, 2, 4, and 6 from subjects in all parts of the study.

Pharmacokinetic samples will also be collected, if possible, immediately following any SAE or any AE leading to discontinuation.

For each individual subject, the PK samples collected at Weeks 2, 4, and 6 (i.e., postdose samples) should be collected at times that vary as much as possible between 2 and 24 hours after dosing within prespecified time intervals. One sample should be collected 2 to 5 hours after dosing, one sample should be collected 5 to 8 hours after dosing, and one sample should be collected 8 to 24 hours after dosing. If this is not possible and samples at two different visits must be collected within the same time interval after dosing, then these should vary within the interval to provide as much variation as possible overall. PK sample collection times will depend on both dose timing and clinic visit timing. Because subjects may take their dose at home or in clinic on these visit days, and sites may schedule the times of these visits to target desired PK sample collection times, PK sample collection should not require excessively long stays at the clinic.

For all post-baseline PK samples (scheduled and unscheduled), the dates and times of administration of the last three doses of study drug should be recorded, as well as the date and time of the sample draw. The baseline PK sample will be taken predose.

6.5 Additional Biomarkers for Alzheimer's Disease

A blood draw will be performed, for eligible subjects in all parts of the study, at Visit 2 (Baseline) to collect blood for testing additional biomarkers related to Alzheimer's disease not used for eligibility (Section 6.1.4).

6.6 Optional Exit Interviews with Caregivers

Optional individual interviews may be conducted with approximately 40 caregivers of subjects from US sites of ACP-204-006 Part 1, Part 2A, and Part 2B. Caregivers of subjects who complete the study or terminate early will be eligible to participate in an interview.

Caregivers will review a consent form describing the optional exit interviews and provide consent or not at any applicable study visit, but it must be obtained no later than Visit 6 (EOT/ET). The interviews will be conducted by experienced qualitative interviewers from an independent and neutral third party, using a semi-structured interview guide. The interviews will be conducted by telephone/web-based audio within approximately 2 weeks after the EOT or ET visit, as indicated in the schedule of assessments (Table S–1). Interviews will last up to approximately 60 minutes.

The objectives of the interviews are to gather caregiver observations of subject experiences with ADP and the study treatment, as well as caregiver perceptions of the meaningfulness of treatment-related changes that may have occurred during the study.

The results of the interviews will be reported separately from the clinical study report.

6.7 Safety Follow-up

A 30-day Safety Follow-up Period, incorporating two telephone calls to the subject and study partner/caregiver, at 7 (±3) days and 30 (+4) days after the last dose of study drug, is to be completed for subjects who complete the Double-blind Treatment Period of the study and decide not to continue into the OLE study or are not eligible for the OLE study, as well as those who discontinue prematurely from the study. Subjects should have the following completed during both telephone calls per Table S–1:

- Assessment of concomitant medications/treatments
- Assessment of AEs
- GCAS
- C-SSRS

The follow-up telephone call at 7 (±3) days after the last dose of study drug should be utilized to evaluate any new adverse events after discontinuation of study drug and any ongoing adverse events.

See Section 4.5.1 for additional information, including limitations in case of withdrawal of consent.

6.8 Early Termination Visit and Mortality Follow-up

Unless consent has been withdrawn, subjects who discontinue before completion of the study should have EOT/ET assessments done at the time of discontinuation (i.e., ET; as outlined in Table S–1). Additional safety assessments may be performed for subjects who discontinue early from the study if deemed by the Investigator to be clinically indicated. The reason for discontinuation should be determined if possible and recorded on the subject's eCRF.

See Section 6.7 for a description of the Safety Follow-up Period that subjects who discontinue prematurely from the study are to complete.

In addition, a telephone call to the subject and/or study partner/caregiver to confirm that the subject is still living should be conducted 30 (+4) days after the subject's intended day of last dose of study drug (i.e., the day that their last dose of study drug would have been taken had they not discontinued prematurely). If a subject has died, every effort will be made where possible to collect the cause of death (including documentation; e.g., death certificate or autopsy report with subject identifiers redacted).

See Section 4.5.1 for additional information, including limitations in case of withdrawal of consent.

6.9 Unscheduled Visits

Unscheduled visits may occur as determined by the Investigator. The following safety assessments generally should be recorded at each unscheduled visit: assessment of AEs, assessment of concomitant medications/treatments, and measurement of vital signs (including orthostatic changes) and weight. The Investigator may perform any additional safety evaluations or any other assessments deemed by the Investigator to be clinically indicated.

6.10 Remote Assessments or Visits

Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when on-site assessments may not be possible. In those cases, assessments (including PK assessments) may be performed at the subject's place of residence either in person, or via video technology or telephone where possible. The Investigator must contact the Medical Monitor for approval with the plan. Sites must keep a log to identify details of all visits that are administered remotely. The location of the collected assessments should be captured in the eCRF.

7 ADVERSE EVENTS

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Event

An AE is defined as "any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to study drug".

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE.

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to Baseline and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) or scheduled surgery/procedure. The condition that leads to the procedure is an AE if not present at time of consent.
- Overdose of concomitant medication without any signs or symptoms will not be considered an AE, but if a subject is hospitalized or has other serious criteria, the overdose will be considered an AE and shall be reported on the Sponsor's Overdose Reporting Form.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a Pregnancy Form

7.1.2 Definition of Serious Adverse Event

In addition to the severity rating, each AE will be classified by the Investigator as "serious" or "not serious." The seriousness of an event will be defined according to the applicable regulations and generally refers to the outcome of an event. An SAE is one that meets one or more of the following:

- Is fatal

- Is life-threatening
- Results in disability or permanent damage
- Requires hospitalization (initial or prolonged)
- Results in congenital anomaly or birth defect
- Other serious event (medically significant/important medical event)

Definition of Life-threatening

A life-threatening event places the subject at immediate risk of death from the event as it occurred. This does not include an AE, which, had it occurred in a more severe form, might have caused death.

Definition of Disability or Permanent Damage

Disability is defined as a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Definition of Hospitalization

Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization.

Examples of visits to a hospital facility that do **not** meet the serious criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery
- Preplanned or elective procedures
- Protocol procedures
- Social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence

Definition of Medically Significant

Important medical events (medically significant events) that may not result in death, be life-threatening, or require hospitalization may be considered to be an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An SAE may also include any other event that the Investigator or Medical Monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

7.1.3 Definition of Adverse Event of Special Interest

An adverse event of special interest (AESI) is a serious or nonserious adverse event that is one of scientific and medical concern specific to the Sponsor's product for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

The AESIs in this study are seizures (see also Section 7.4.5.1), syncope, falls, migraine, and transient ischemic attack (TIA) as assessed by the Investigator. Investigator-reported events of seizures, syncope, falls, migraine, and TIA will be subsequently evaluated by an independent neurologist to ensure that all potential seizures are accounted for in the final clinical study report.

For further details and reporting of AESIs, see Section 7.4.5.

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

The severity of each AE will be assessed as described below and reported in detail as indicated on the eCRF:

- **Mild**: awareness of sign or symptom but easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities
- **Moderate**: sufficiently discomforting to interfere with normal everyday activities
- **Severe**: incapacitating and/or preventing normal everyday activities

7.2.2 Relationship to Study Drug

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related." An event is considered related if there is a reasonable possibility that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Consider the following when assessing causality:

- Temporal associations between the agent and the event
- Response to drug cessation (de-challenge) or re-challenge
- Compatibility with known class effect
- Known effects of concomitant medications
- Pre-existing risk factors
- A plausible mechanism
- Concurrent illnesses

- Past medical history

7.2.3 Duration

The start and stop dates for AEs will be recorded using the following criteria:

- **Start:** Date of the first episode of the AE or date of worsening in severity
- **Stop:** Date when AE recovered or resolved, recovered or resolved with sequelae, or worsened in severity

7.2.4 Frequency

The frequency of the AE should be indicated according to the following definitions:

- **Single:** Experienced once, without recurrence at same severity
- **Recurrent:** More than one discrete episode with the same severity

7.2.5 Action Taken with Study Drug

- **Dose not changed:** No change in study drug
- **Drug interrupted:** Study drug temporarily stopped
- **Drug withdrawn:** Study drug discontinued permanently
- **Not applicable**
- **Unknown**

7.2.6 Therapy

- **None:** No new treatment instituted
- **Medication:** New treatment initiated as a direct result of AE
- **Other:** Other action required

7.2.7 Outcome

- **Recovered/resolved:** Recovered or resolved
- **Recovered/resolved with sequelae:** Recovered or resolved with sequelae
- **Not recovered/not resolved:** Not recovered or not resolved
- **Fatal:** Death due to an AE
- **Unknown:** Unknown

7.2.8 Seriousness

- **Not serious**
- **Serious** (see Section 7.1.2)

7.2.9 Definition of Unexpectedness

An AE, the nature or severity of which is not consistent with the information provided in the Reference Safety Information section of the current ACP-204 Investigator's brochure.

7.3 Time Period and Frequency for Event Assessment and Follow-up

For subjects who roll over into the OLE study, AEs for this study will be recorded from the time informed consent is obtained in this study until the first dose of study drug in the OLE study.

For subjects who discontinue from the study or do not roll over into the OLE, AEs will be recorded from the time informed consent is obtained through the study Safety Follow-up Period.

If an AE is ongoing at the end of the study Safety Follow-up Period, every reasonable attempt should be made to follow and appropriately treat the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable.

In the event that a subject discontinues from the study and has an ongoing AE at the time of discontinuation (Section 4.5.1), the subject should be followed and appropriately treated until the AE resolves or until the Investigator deems the AE to be chronic or stable. If a subject or LAR withdraws consent from the study because of an AE, no additional assessments may be performed (Section 4.4).

For subjects who discontinue from the study and have not withdrawn consent (or had consent withdrawn by LAR) from further data collection, a telephone call to the subject and/or study partner/caregiver to confirm that the subject is still living will be conducted 30 (+4) days after the subject's intended day of last dose of study drug (i.e., the day that their last dose of study drug would have been taken had they not discontinued prematurely). If a subject has died, every effort will be made to collect cause of death information where possible (including documentation; e.g., death certificate or autopsy report with subject identifiers redacted).

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

The Investigator must record all observed AEs and all reported AEs. At each visit, the Investigator should ask the subject a nonspecific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any AEs have been experienced since the last report or visit.

Note that any use of medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an AE that may need to be recorded on both the AE and the concomitant medication page.

All AEs, serious and not serious, will be recorded on the AE eCRF page using appropriate medical terminology. Severity and relationship to study drug will be assessed by the Investigator.

When possible, clinical AEs should be described by diagnosis and not by symptoms (e.g., “cold” or “seasonal allergies” instead of “runny nose”).

All AEs, *whether or not related to the study drug*, must be fully and completely documented on the AE eCRF and in the subject’s notes.

7.4.2 Serious Adverse Event Reporting

The reporting of SAEs by the Sponsor or designee to the regulatory authorities is a regulatory requirement. Each regulatory authority has established a timetable for reporting SAEs based upon established criteria.

When an SAE occurs, Investigators will review all documentation related to the event and will complete the SAE Form with all required information (initial and updated/follow-up information, including resolution of event, if applicable) and send (within 24 hours of discovery) as per the contact information provided on the SAE Form, as well as enter the SAE into the EDC system in a timely manner.

At a minimum, events identified by the Sponsor that require expedited reporting as serious, unexpected, and related to study drug must be brought to the attention of the responsible IRB/EC, as per applicable regulations. These will be provided by the Sponsor after their assessment. For European Union member states, the Sponsor or its designee will provide reports of SUSARs directly to the ECs, as required by local legislation. In all other countries, it is the Investigator’s responsibility to provide these expedited reports to the responsible IRB/EC. It is also the Investigator’s responsibility to notify the responsible IRB/EC regarding any new and significant safety information.

Unless they roll over into the OLE, subjects will be followed through the Safety Follow-up Period (i.e., 30 [+4] days after last dose of study drug) for any SAEs and/or other reportable information until such events have resolved or the Investigator deems them to be chronic or stable. SAE updates/follow-up and resolution also require an updated SAE Form to be sent within 24 hours of discovery or discovery of resolution, respectively.

In the event of any SAE (other than death), the study subject will be instructed to contact the Investigator (or designee) using the telephone number provided in the ICF. All subjects experiencing an SAE will be seen by the Investigator or designee as soon as is feasible following the report of the SAE.

Serious AEs occurring after the Safety Follow-up Period (i.e., 30 [+4] days after last dose of study drug) should be reported if in the judgment of the Investigator there is "a reasonable possibility" that the event may have been caused by the study drug.

SAEs should also be reported to the IRB/EC according to local regulations.

7.4.3 Reporting of Pregnancy

Any female subject who becomes pregnant during the study (with or without AEs) must be discontinued from the study. If the pregnancy occurred after exposure to the study drug, it must be reported on the Pregnancy Form within 24 hours of discovery to the Sponsor or its designee. Any female subject who becomes pregnant during the study will be followed through the pregnancy outcome.

If pregnancy occurs during the study, the pregnant subject should be unblinded so that counseling may be offered based on whether the fetus was exposed to the active study drug or placebo.

Any AEs that are the consequence of pregnancy and which meet the criteria for serious should also be reported via the SAE Form.

7.4.3.1 Reporting Paternal Study Drug Exposure

Paternal study drug exposure is defined as a father's exposure to a medicinal product before or during his partner's pregnancy. Any paternal study drug exposure cases must be reported to the Sponsor within 24 hours of discovery via the Pregnancy Form. Any AEs that are the consequence of paternal study drug exposure and which meet the criteria for serious must also be reported to the Sponsor within 24 hours of discovery via the SAE Form.

7.4.4 Reporting of Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported to the Sponsor or designee on the Sponsor's Overdose Reporting Form within 24 hours of discovery. In addition, all events of overdose are to be captured as protocol deviations (see Section 5.1.7).

7.4.5 Reporting of Adverse Events of Special Interest

Adverse events of special interest in this study are seizures, syncope, falls, migraine, and TIA as reported by the Investigator (Section 7.1.3). When an AESI occurs, it must be reported within 24 hours of discovery to the Sponsor or its designee using both the AESI Additional Information Form and the SAE Form, as well as entered in the EDC in a timely manner. The SAE Form must be used even if the event (other than seizure, which is always an SAE) is not considered serious. Both forms should be sent to the Sponsor or its designee as per the contact information on the

SAE Form to meet expedited reporting requirements, as applicable. The information included on the SAE Form will determine whether an event other than seizure is categorized as an SAE. The investigator-reported events of seizures, syncope, falls, migraine, or TIA will be summarized in the primary safety listings and tables of the study.

In order to ensure that all potential seizures are identified during the course of the study, a blinded, independent neurologist will evaluate the case report forms for AESIs, as well as other blinded safety information in the EDC. Neurologist-evaluated events will be listed and summarized separately in supplemental tables in the final study report and will not contribute to expedited reporting, which will be based upon Investigator reporting only. Neurologist evaluations will not override or replace Investigator characterizations of AESIs.

7.4.5.1 Reporting of Seizures

Any seizure activity that occurs during the study is an AESI and should be considered serious (e.g., medically important). The following information shall be collected and reported within 24 hours of discovery to the Sponsor using both the AESI Additional Information Form and the SAE Form for both initial and follow-up reporting, as well as entered in the EDC system in a timely manner, as per Section 7.4.2 and Section 7.4.5:

- A complete description of the event, including but not limited to: loss or alteration of consciousness, the area of the body involved, semiology of the event, loss of bladder/bowel control, tongue biting (including the area of the tongue bitten), presence of aura (or any other premonitory symptoms)
- The presence of any triggers/precipitating factors, such as fever, dehydration, change in postural position, ongoing phlebotomy
- Any predisposing factors not identified at Screening (e.g., history of head trauma)
- Any previous history of seizures not identified at Screening (including febrile seizures)
- Any pertinent laboratory abnormalities (such as electrolytes, glucose, BUN, CR, and CBC with differential abnormalities) or any other signs of systemic illness. Relevant laboratory tests should be run as close as possible to the time of seizure activity, and the results should be entered into the EDC system or otherwise available for review as soon as possible.
- A urine sample for urine drug test as well as a blood sample to measure blood alcohol levels shall be collected as close as possible to the time of seizure activity. The results of the urine drug test and blood alcohol test shall be entered into the EDC system or otherwise available for review as soon as possible. If collection of a urine sample proves impractical or impossible (e.g., because the subject is incontinent) controlled substances will be tested from a blood sample where local regulations permit this.

8 MONITORING

Routine monitoring of study sites is described in Section 11.2.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol and amendment(s) as applicable, with GCP, and with applicable regulatory requirements. Details of the study site monitoring process are described in a separate clinical monitoring plan document.

9 STATISTICAL METHODS AND DATA ANALYSIS

Statistical methods will be documented in detail in a statistical analysis plan (SAP) for Part 1, and a separate SAP for each of independent Part 2A and Part 2B, to be approved by the Sponsor prior to unblinding and database lock for the respective parts of the study. Deviations from the approved SAPs will be described and justified in the clinical study report(s).

9.1 Statistical Hypothesis

The primary endpoint is change from Baseline in the SAPS-H+D total score at Week 6. The primary endpoint will be compared between each of the ACP-204 dose groups (30 mg, 60 mg) and the placebo group.

Let Δ be the difference in the mean change from Baseline in the SAPS-H+D total score at Week 6 between the ACP-204 group and the placebo group:
The null hypothesis for the primary endpoint is: $\Delta = 0$
The alternative hypothesis for the primary endpoint is: $\Delta \neq 0$

The key secondary endpoint is CGI-I-ADP score at Week 6; it will be compared between each of the ACP-204 dose groups (30 mg, 60 mg) and the placebo group.

Let Δ be the difference in the mean at Week 6 in the CGI-I-ADP score between the ACP-204 group and the placebo group:
The null hypothesis for the key secondary endpoint is: $\Delta = 0$
The alternative hypothesis for the key secondary endpoint is: $\Delta \neq 0$

9.2 Multiplicity Adjustment

In order to control the overall type I error rate, the multiplicity will be adjusted for multiple comparisons of 30 mg versus placebo and 60 mg versus placebo for the primary endpoint and key secondary endpoint. Details of the multiplicity control procedure will be provided in the SAP.

9.3 Sample Size Determination

Part 1:

In Part 1, approximately 318 subjects will be randomized in a 1:1:1 ratio to ACP-204 60 mg (n=106), ACP-204 30 mg (n=106), or placebo (n=106). After allowance of 5% non-evaluable subjects, at least 100 evaluable subjects will be randomized per treatment group. This will provide at least 80% power to detect a standard effect size 0.4 between either ACP-204 dose (n=100) and placebo (n=100) at an alpha level of 0.05 using a two-sided test.

Part 2A and Part 2B:

In each of Part 2A and Part 2B of the study, approximately 378 subjects will be randomized in a 1:1:1 ratio to ACP-204 60 mg (n=126), ACP-204 30 mg (n=126), or placebo (n=126), to include at least 360 evaluable subjects after allowance of 5% non-evaluable subjects. These 360 subjects, with two active ACP-204 doses should provide at least 85% power to detect a standard effect size 0.4 between either ACP-204 dose (n=120) and placebo (n=120) at an alpha level of 0.05 using a two-sided test.

9.4 Descriptive Statistics

Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For each categorical outcome, the number and percentage of subjects in each category will be reported.

9.5 Missing Data

Handling of missing values will be described in detail in the SAP. Sensitivity analyses will be performed to assess the impact of missing data on the robustness of primary analysis results.

9.6 Analysis Sets

Part 1 of Study ACP-204-006 will be locked, unblinded, and analyzed while Part 2A and Part 2B are ongoing.

Part 2A or Part 2B will be analyzed independently from each other and independently from the Part 1 analysis.

The Randomized Analysis Sets of Part 1, Part 2A, and Part 2B include all subjects who were randomized in Part 1, Part 2A, or Part 2B, respectively.

The Randomized Analysis Sets will be used for analyses specified in the SAP based on the randomized treatment assignment.

The Safety Analysis Sets of Part 1, Part 2A, and Part 2B include all randomized subjects in Part 1, Part 2A, or Part 2B, respectively, who received at least one dose of study drug (ACP-204 or placebo). Subjects will be analyzed based on the treatment they actually received.

The Safety Analysis Sets will be used for all safety analyses.

The Full Analysis Sets of Part 1, Part 2A, and Part 2B include all randomized subjects in Part 1, Part 2A, or Part 2B, respectively, who received at least one dose of study drug and who have both a baseline value and at least one post-baseline value for SAPS-H+D total score. Subjects will be analyzed based on their planned randomized treatment.

The Full Analysis Sets will be used for the analysis of all efficacy endpoints.

The PK Analysis Set includes all subjects in the Safety Analysis Set who have sufficient PK data to derive at least one PK parameter.

Any other analysis sets, if necessary, will be defined in the SAP.

9.7 Efficacy Analyses

All efficacy endpoints will be analyzed and summarized by treatment group using the Full Analysis Set of Part 1 and the Full Analysis Sets of independent Part 2A and Part 2B, respectively. The Full Analysis Sets of Part 2A and Part 2B will be analyzed separately from each other and independently from the Full Analysis Set of Part 1.

All efficacy endpoints will be summarized by treatment group using descriptive statistics.

All efficacy statistical tests will be two-sided hypothesis tests performed at an alpha level of 0.05. In addition, all confidence intervals will be two-sided 95% confidence intervals, unless stated otherwise.

9.7.1 Estimand

The primary estimand defining the treatment effect of interest in this study uses the hypothetical strategy specified in the ICH E9 (R1) Addendum. The estimand, or target of estimation, following the hypothetical strategy is the pharmacological effect seen, had no study treatment discontinuation occurred. This hypothetical estimand is justifiable in this case, since the focus is on the pharmacological effect of the drug additional to non-specific effects. Subjects who discontinue from a study treatment either could have lost their treatment effect, had the subjects not taken any other symptomatic medication after the discontinuation of study treatment, or could have had their treatment effect masked, had the subjects taken other symptomatic medication after the discontinuation of study treatment. This means that any observations taken after subjects stop study medication will most likely not contribute relevant information about the pharmacological effect of the study drug.

By this strategy, the last collected efficacy assessment after premature treatment discontinuation will be done only at the ET visit. Every effort will be made to complete the ET evaluations prior to administering any additional medications for the treatment of ADP or other prohibited medications. In the case of lost to follow-up events or death, no ET evaluations are expected, and only scheduled assessments performed before such an event are expected.

In this hypothetical strategy, the event of premature discontinuation of study medication is considered missing at random (MAR), and the primary endpoint of the study could be considered as a combination of the responses of on-treatment completers at Week 6 and the imputation of the endpoint to Week 6 following the trend in each treatment group using the mixed-effect model repeated measures (MMRM) method for subjects who discontinuation study drug during the study. All data collected during the study treatment period will be used for statistical analysis. Under the MAR assumption, MMRM provides an unbiased estimate of treatment effect for the treatment period.

The primary estimand for this study is defined by the following components:

a. **Target population**: Full Analysis Set
b. **Variable (primary endpoint):** Mean change from Baseline to Week 6 in the SAPS-H+D total score
c. **Treatment condition**: ACP-204 60 mg, ACP-204 30 mg, or placebo
d. **Intercurrent events**: Premature treatment discontinuation; the hypothetical estimand is to evaluate the pharmacological effect as if no treatment discontinuations had occurred.
e. **Measure of intervention effect**: Difference in endpoint means between ACP-204 and placebo arms as if had no subject discontinued the treatment

9.7.2 Primary Estimator

The primary endpoint is the change from Baseline in the SAPS-H+D total score at Week 6. The primary analysis will evaluate treatment effect of ACP-204 60 mg and ACP-204 30 mg compared to placebo based on the Full Analysis Set using the MMRM. The model will include effects for treatment groups, visit, treatment-by-visit interaction, baseline SAPS-H+D total score-by-visit interaction, and randomization stratification factors (site, institution status [yes or no]). An unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The treatment effect will be estimated by the difference in least squares means of SAPS-H+D total score at Week 6 and will be tested at an alpha level of 0.05 (two-sided) using the Full Analysis Set of Part 1 and Full Analysis Sets of Part 2A and Part 2B, respectively. The difference in least squares means, corresponding 95% confidence interval, and p-value will be reported.

9.7.3 Key Secondary Endpoints Analyses

The key secondary efficacy endpoint, CGI-I-ADP score at Week 6, will be analyzed in a similar fashion as the primary endpoint. The model will include effects for treatment groups, visit, treatment-by-visit interaction, randomization stratification factors (site, institution status [yes or no]), baseline CGI-S-ADP score, and baseline CGI-S-ADP score-by-visit interaction. The

treatment effect will be estimated by the difference in least squares means of CGI-I-ADP score at Week 6 and will be tested at an alpha level of 0.05 (two-sided) using the Full Analysis Set of Part 1 and Full Analysis Sets of Part 2A and Part 2B, respectively. The difference in least squares means, corresponding 95% confidence interval, and p-value will be reported.

9.7.4 Other Secondary and Exploratory Endpoints Analyses

The other secondary and exploratory efficacy endpoints are listed in Section 2.2.2.1 and Section 2.3.1, respectively.

For analysis of continuous efficacy endpoints, the analysis method will be the same as that used for the primary variables, except for QOL-AD score and SDI score. The QOL-AD score and SDI score will be analyzed using analysis of covariance. For analysis of categorical variables in other secondary efficacy endpoints (e.g., proportional analysis), the Cochran Mantel Haenszel approach stratified by the randomization strata will be used. All other (i.e., not key) secondary and exploratory efficacy analyses will be performed using the Full Analysis Set of Part 1 and Full Analysis Sets of Part 2A and Part 2B, respectively.

9.8 Safety Analyses

All safety analyses will be performed using the Safety Analysis Set of Part 1 and Safety Analysis Sets of Part 2A and Part 2B, respectively. Safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug, unless specified otherwise, will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints.

The safety endpoints are (Section 2.4.1):

- TEAEs
- 12-lead ECGs
- Vital signs, including orthostasis assessment
- Weight and BMI
- Physical examination results
- Clinical laboratory tests
- GCAS score
- C-SSRS
- UKU Sleepiness/Sedation and Orthostatic Dizziness scores
- MMSE score
- DSST score

- ESRS-A scores

9.8.1 Adverse Events

All AEs will be classified into standard terminology using the Medical Dictionary for Regulatory Activities coding dictionary.

Treatment-emergent adverse events are:

- Any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug

All AEs will be listed, and TEAEs will be summarized by system organ class and preferred term. Treatment-emergent adverse events, TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, serious TEAEs, and serious TEAEs related to study drug will all be summarized by treatment group. Adverse events of special interest (AESIs) will be summarized by treatment group as well. Investigator-reported AESIs will populate the primary safety table, and neurologist-evaluated events will be summarized separately in supplemental safety tables in the final study report.

Deaths of subjects who discontinue prematurely from the study that occur between 30 days after the last dose of study drug and 30 days after the subject's intended day of last dose of study drug will be summarized separately.

9.8.2 ECGs, Vital Signs, Weight and BMI, Physical Examination Results, and Clinical Laboratory Tests

Descriptive statistics for ECG, vital signs and weight, and clinical laboratory parameters, including change from Baseline, will be tabulated by visit and treatment group. The results of the physical examinations at each visit will be tabulated by treatment group. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines and based on the US Food and Drug Administration (FDA) E14 Guidance Document.

The number and percentage of subjects with potentially clinically important post-baseline values will be summarized for selected parameters. The criteria for potentially clinically important values will be specified in the SAP.

9.8.3 GCAS, C-SSRS, UKU Sleepiness/Sedation and Orthostatic Dizziness, MMSE, DSST, and ESRS-A

UKU Sleepiness/Sedation and Orthostatic Dizziness, MMSE, DSST, and ESRS-A scores and changes from Baseline will be summarized by treatment group and visit and will be analyzed using an MMRM model similar to the primary analysis. For the GCAS, the number and

percentage of subjects with a score of 3 or 4 during the study will be tabulated. For the C-SSRS, the summary descriptive statistics will be tabulated.

9.9 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

The PK and PK/PD endpoints are ACP-204 PK parameters using a population PK approach and PK/PD of ACP-204 using appropriate PK/PD analysis methods.

Plasma concentration data for ACP-204 will be listed and summarized using descriptive statistics. Results will be used for other analyses (e.g., population PK and PK/PD modeling), which will be presented in a separate report(s). ACP-204 metabolites will be summarized where appropriate.

Guided by exploratory analyses, PK/PD models to describe the exposure-response relationship between ACP-204 exposure parameters and the relevant efficacy and safety endpoints will be developed using appropriate PK/PD methods. Results will be presented in a separate report per a prespecified data analysis plan.

ACP-204 plasma concentration data will remain blinded until unblinding of the clinical database for each respective part of the study.

9.10 Subgroup Analyses

Selected analyses may be performed in subgroups defined in the SAP.

9.11 Interim Analyses

No interim analyses are planned for this study. The planned analysis for Part 1 is not considered an interim analysis. It will occur only after all subject participation in Part 1 is complete.

9.12 Data and Safety Monitoring Board

An external DSMB will review interim safety data, including data on AEs, SAEs, and safety laboratory data. The DSMB will be independent of the Sponsor and the Investigators and will be empowered to recommend whether the study should be terminated due to safety concerns, continue as planned, or continue with modification.

The DSMB may review blinded, unblinded, or partially unblinded data, but the Sponsor and the Investigators will remain blinded to the data provided to the DSMB until the official unblinding of the databases. In cases where the DSMB reviews unblinded data, the treatment codes will be released to an independent statistician/programmer to produce unblinded statistical outputs provided only to the DSMB.

The DSMB membership, activities, responsibilities, and frequency of meetings will be described separately in the DSMB charter.

While the DSMB will be making recommendations regarding future conduct of the study, the Sponsor retains final decision-making authority on all aspects of the study.

10 STUDY MANAGEMENT AND DATA COLLECTION

10.1 Data Collection and Management Responsibilities

All documents required for the conduct of the study as specified in the ICH E6 (GCP) guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory authorities.

To safeguard data integrity, the Investigator, site staff, and service providers delegated by the Investigator/institution must follow the "ALCOA+" principles, ensuring that data should be "Attributable, Legible, Contemporaneous, Original, and Accurate." The "+" indicates that data is also "Complete, Consistent, Enduring, and Available."

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC direct access to source documents (such as original medical records, both in paper format and in electronic systems, where applicable) as allowed by local regulations. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are needed for the evaluation of the study, either in person or through remote video/electronic medium (such as email) if applicable. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

10.2 Source Documents

All study specific information obtained at each study visit must be recorded in the subject's record (source documentation), and then entered into a validated EDC database by trained site personnel and/or transferred electronically into EDC or another secure data repository. The source documentation may consist of source notes captured by site personnel, as well as laboratory reports, ECG reports, electronic source data, electronic clinical outcomes assessments, and rating scales platforms.

10.3 Clinical Data

Subject data required by this protocol are to be recorded in an EDC system on eCRFs and/or transferred electronically and securely for data review. The Investigator and his or her site personnel will be responsible for completing the eCRFs. The Investigator is responsible for the accuracy and reliability of all the information recorded on the eCRFs and captured as source. All information requested on the eCRFs needs to be supplied, including subject identification data, visit date(s), assessment values, etc., and any omission or discrepancy will require explanation.

All information on eCRFs must be traceable to source documentation (unless eCRF is considered the source) at the site.

10.4 Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs, medical records, or other documents submitted to the Sponsor or designees, subjects must be identified by a subject identification number only. Subject identifiers uniquely identify subjects within the study and do not identify any person specifically. Documents that are not de-identified (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH E6 (GCP) guidelines and as such, should not be submitted to the Sponsor or designees. These documents should remain accessible on site (Section 10.1). Data collection and handling should comply with the European Union General Data Protection Regulation (EU GDPR) and other relevant regulations concerning data privacy, where applicable. Acadia has assigned a Data Protection Officer (DPO) as per the EU GDPR.

10.5 Study Records Retention

Investigators are required to maintain all essential study documentation as per ICH E6 (GCP) guidelines. This includes, but is not limited to, copies of signed, dated and completed eCRFs, documentation of eCRF corrections, signed ICFs, audio recordings, subject-related source documentation, and adequate records for the receipt and disposition of all study drug. Investigators should maintain all essential study documentation, for a period of at least 2 years following the last approval of marketing application in an ICH region (US, Europe, and Japan), or until at least 2 years after the study drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. Only the Sponsor can notify an Investigator or vendor when any records may be discarded. Investigators should contact the Sponsor before destroying any files.

10.6 Protocol Exceptions and Deviations

No prospective entry criteria protocol deviations are allowed; all subjects must meet all eligibility criteria in order to participate in the study.

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's post-enrollment participation in the study it is discovered that the subject did not meet all eligibility criteria, except where related to clinical laboratory results at Baseline or central cardiologist interpretation of ECG QTcF at Baseline, this will be reported as a major protocol deviation. In this situation, including where related to clinical laboratory results at Baseline or central cardiologist interpretation of ECG QTcF at Baseline, the subject will be discontinued from the study, unless the discontinuation presents an unacceptable medical risk.

The justification to allow the subject to continue in the study will be made by the Sponsor, with medical input from the Investigator, and will be documented. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.7). The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

10.7 Protocol Amendments

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/EC in accordance with local requirements and, if required, to regulatory authorities, as either an amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the changes involve only logistical or administrative aspects of the study. No approval is required for notifications.

10.8 Serious Breach Reporting

A “serious breach” is any deviation from the approved protocol version or the clinical trial regulation likely to affect to a **significant** degree the safety and/or rights of a subject or the reliability and robustness of the data generated in the clinical study.

The Investigator, site staff, and service providers delegated by the Investigator/institution must identify the occurrence of a (possible or suspected) serious breach and immediately report to the Sponsor at seriousbreachrandd@acadia-pharm.com or (+1) 858-558-2871, Press 2.

11 QUALITY MANAGEMENT

11.1 Quality Risk Management

The Sponsor utilizes the ICH E6 (GCP) quality risk management approach that includes methods to assure and control the quality of the study proportionate to the risks inherent in the study and the importance of the information collected. The intent is that all aspects of this study are operationally feasible and that any unnecessary complexity, procedures, and data collection are avoided. The Sponsor’s risk management approach includes the following documented activities:

- Critical process and data identification: during protocol development, risks of processes and data that are critical to ensure human subject protection and the reliability of study results are identified and assessed and, where applicable, quality tolerance limits (QTLs) are defined.
- Risk identification: risks to critical study processes, governing systems, study drug, study design, data collection, and recording are identified.

- Risk evaluation: identified risks are evaluated by considering the following factors: (a) likelihood of occurrence, (b) impact on human subject protection and data integrity, and (c) detectability of errors.
- Risk control: risks that can be avoided, reduced (i.e., mitigated), or accepted are differentiated. Risk mitigation activities are incorporated in protocol design and implementation, study plans, training, processes, and other documents governing the oversight and execution of study activities. Where possible, predefined quality tolerance limits are defined to identify systematic issues that can impact subject safety or data integrity and deviations from the predefined quality tolerance limits will trigger an evaluation and possibly an action. Contingency plans are developed for issues with a high risk factor that cannot be avoided.
- Periodic risk review, communication, and escalation of risk management activities during study execution and risk outcome reporting in the clinical study report (CSR).

11.2 Quality Control and Quality Assurance

The Sponsor or designees and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Sponsor's or designee's monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records (both in paper format and in electronic systems, where applicable) needed to verify the entries on the eCRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH E6 (GCP) guidelines and the Sponsor's audit plans, sites participating in this study may be audited. These audits may include a review of site facilities (e.g., pharmacy, drug storage areas, and laboratories) and review of study-related records may occur in order to evaluate the study conduct and compliance with the protocol, ICH E6 (GCP) guidelines, and applicable regulatory requirements.

The Sponsor's or designee's representatives, regulatory authority inspectors and IRB/EC representatives who obtain direct access to source documents should also respect subject confidentiality, taking all reasonable precautions in accordance with applicable regulatory requirements to maintain the confidentiality of subjects' identities.

12 ETHICAL CONSIDERATIONS

12.1 Ethical Standard

The study will be conducted in compliance with the protocol, the Declaration of Helsinki, applicable ICH E6 (GCP) guidelines, and other applicable regulatory requirements (e.g., serious breach reporting [Section 10.8], urgent safety measures, EU Clinical Trial Regulation, and EU GDPR).

The study will be performed in accordance with current US Health Insurance Portability and Accountability Act (HIPAA) regulations, applicable US FDA GCP Regulations, and ICH E6 (GCP) guidelines and clinical safety data management (E2A).

As per ICH E6 (GCP), whether the study is completed or prematurely terminated, a clinical study report will be prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The clinical study report, if part of a marketing application, shall meet the standards of the ICH Guidance for Structure and Content of Clinical Study Reports (E3) and follow the process as outlined in Acadia's standard operating procedure.

The CSR will be signed by Acadia and the Coordinating (or Principal) Investigator, as per standard operating procedure, unless decided otherwise by Acadia.

12.2 Institutional Review Board/Ethics Committee

The Investigator or designee will provide the IRB/EC with all requisite material, including a copy of the protocol, informed consent, the Investigator's brochure for the study drug, any subject information or advertising materials, and any other requested information. The study will not be initiated until the IRB/EC provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Investigator and copies received by the Sponsor. All amendments will be sent to the IRB/EC for information (minor amendment) or for submission (major amendment) before implementation. The Investigator will supply the IRB/EC and the Sponsor with appropriate reports on the progress of this study, including any necessary safety updates, in accordance with the applicable government regulations and in agreement with policy established by the Sponsor.

12.3 Informed Consent/Assent Process

Properly executed, written informed consent must be obtained from each subject or subject's LAR prior to any screening procedures. When a subject lacks capacity to consent, and consent is being provided by an LAR, subject assent for participation must be documented per local regulations. The subject's study partner/caregiver must also provide written consent prior to any screening procedures.

The informed consent must, at a minimum, include the elements of consent described in ICH E6 (GCP) and the US CFR 21 part 50.25. A copy of the ICF planned for use will be reviewed by the Sponsor or designee for acceptability and must be submitted by the Investigator or designee together with the protocol, to the appropriate IRB/EC for review and approval prior to the start of the study at that investigational site. Consent forms must be in a language fully comprehensible to the prospective subject, LAR (if applicable), and study partner/caregiver. The Investigator must provide the Sponsor or designee with a copy of the IRB/EC letter approving the protocol and the ICF before the study drug supplies will be shipped and the study can be initiated.

The consent form must be revised if new information becomes available during the study that may be relevant to the subject's willingness to continue participation. Any revision must be submitted to the appropriate IRB/EC for review and approval in advance of use.

12.3.1 Consent and Other Informational Documents Provided to Subjects

The subject and/or LAR must be given a copy of the signed informed consent and the original maintained in the designated location at the site.

12.3.2 Consent Procedures and Documentation

It is the Investigator or designee's responsibility to obtain written informed consent from the subject and/or LAR after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The subject and/or LAR must be given ample time to decide about study participation and opportunity to inquire about details of the study. The IRB/EC-approved consent form must be personally signed and dated by the subject or LAR with subject assent per local regulations and by the person who conducted the informed-consent discussion. The Investigator or appropriate site personnel must document the details of obtaining informed consent in the subject's study documents.

The subject's study partner/caregiver must also indicate their understanding of the study and their role as a study partner/caregiver to the subject during the study. The subject's study partner/caregiver must provide written consent prior to any Screening visit procedures being performed indicating their agreement to participate in the study in the study partner/caregiver role.

Participation in the caregiver interview is optional. Informed consent must be obtained by the Investigator (or designee), as appropriate, prior to the interviewer contacting the caregiver and conducting the optional caregiver interview.

Records related to a study subject's participation will be maintained and processed according to local laws, and where applicable, the EU GDPR. The consent and study information

documentation will include statements describing local and regional requirements concerning data privacy, and who to contact for questions.

13 PUBLICATION PLAN

All publication rights are delineated in the clinical study agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

14 CONFLICT OF INTEREST POLICY

14.1 Finance, Insurance, and Indemnity

Arrangements for finance, insurance, and indemnity are delineated in the clinical study agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

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16 APPENDICES

Appendix A NIA-AA Guidelines for All-cause Dementia and Alzheimer's Disease

All-cause Dementia

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
    a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
    b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
    c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
    d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
    e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors

Probable Alzheimer's Disease Dementia

Meets criteria for all-cause dementia (see above) and in addition, has the following characteristics:

1. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
2. Clear-cut history of worsening of cognition by report or observation; and
3. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
    a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
    b. Nonamnestic presentations:
        i. Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
        ii. Visuospatial presentation: The most prominent deficits are in spatial

cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

iii. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

4. The diagnosis of probable AD dementia should not be applied when there is evidence of
   a. substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
   b. core features of dementia with Lewy bodies other than dementia itself; or
   c. prominent features of behavioral variant frontotemporal dementia; or
   d. prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
   e. evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Possible Alzheimer's Disease Dementia

A diagnosis of possible AD dementia should be made in either of the circumstances mentioned in the following paragraphs.

Atypical course

Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline,

OR

Etiologically mixed presentation

Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

Source: McKhann et al. 2011

Abbreviations: AD=Alzheimer's disease; NIA-AA=National Institute on Aging-Alzheimer's Association

Appendix B Revised Criteria for Psychosis in Major or Mild Neurocognitive Disorder

A. *Characteristic Symptoms*
Presence of one (or more) of the following symptoms:
1. Visual or auditory hallucinations (e.g., seeing silent individuals standing in the room, seeing children in the yard, or seeing animals in the house)
2. Delusions (fixed false beliefs that the patient believes to be true, e.g. that the spouse is unfaithful, that possessions are being stolen, or that one is not who one claims to be)

B. *Primary Diagnosis*
All the criteria for any major and mild neurocognitive disorder are met, with the etiologic diagnoses specified (e.g., major neurocognitive disorder (Alzheimer's disease)). Specific diagnoses include Alzheimer's disease, dementia with Lewy bodies, vascular dementia, Parkinson disease dementia, frontotemporal dementia, progressive supranuclear palsy, mild cognitive impairment, traumatic brain injury, and corticobasal degeneration. Other rarer causes of major and mild neurocognitive disorder are also appropriate when diagnosed as a cause of psychosis.

C. *Chronology of the onset of symptoms of psychosis vs. onset of symptoms of cognitive impairment*
There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia

D. *Duration*
The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer.

E. *Severity*
Symptoms are severe enough to cause some disruption in patients' and/or others' functioning or pose a threat to the safety of self or others.
"Disruption" is defined as interfering with the patient's or others' ability to accomplish activities of daily living or interact as usual socially; "patient's functioning" is defined as being able to interact with family members and others, not being preoccupied with hallucinations, etc.; "other's functioning" is defined as interfering with the ability of others to care for or interact with the patient or causing distress to the partner.

F. *Exclusionary Criteria*
A diagnosis of psychosis in major or mild neurocognitive disorder should be excluded in the following patients:
1. Patients who have met the criteria for Schizophrenia, Schizoaffective Disorder, Delusional Disorder, Mood Disorder with Psychotic Features, or Depression with Psychotic Features.
2. When the psychosis occurs exclusively during the course of a delirium.
3. When the psychosis is solely attributable to another general-medical condition (e.g., hypothyroidism) or direct physiological effects of a substance (e.g., a drug of abuse, a medication).
4. When the symptoms are culturally appropriate (e.g., ancestor hallucinations in some cultures).
5. When the hallucinations are more readily attributable to conditions known to cause hallucinations such as epilepsy, migraine, disease of the sensory organs, or stroke.

G. *Associated features: (Specify if associated)*
With Agitation: when there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression.
With Depression: when prominent depressive symptoms, such as depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death are present (note that Mood Disorder with Psychotic Features is an exclusion for the diagnosis of psychosis with major or mild neurocognitive disorders (see F.1 above)

Source: Cummings et al. 2020

Appendix C New York Heart Association Classification of Heart Failure

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: American Heart Association

Appendix D Canadian Cardiovascular Society Angina Grading Scale

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Source: Campeau 1976

Appendix E Predictors Composing the PHASES Aneurysm Rupture Risk Score

PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7.0 mm	0
7.0-9.9 mm	3
10.0-19.9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

Source: Greving et al. 2014

Abbreviations: ACA=anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery); ICA=internal carotid artery; MCA=middle cerebral artery; Pcom=posterior communicating artery; posterior=posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery); SAH=subarachnoid hemorrhage

Note: To calculate the PHASES risk score for an individual, the number of points associated with each indicator can be added up to obtain the total risk score.

Appendix F Prohibited and Restricted Concomitant Medications

Subjects who must take prohibited medications will not be eligible for the study.

Subjects who require current treatment with a prohibited medication will be discontinued from the study.

Subjects who have previously taken a prohibited medication will be discontinued from the study unless:

- the prohibited medication has been discontinued AND
- discontinuation from the study presents an unacceptable medical risk to the subject

The justification to allow the subject to continue in the study will be made by the Sponsor/Medical Monitor with medical input from the Investigator, and will be documented. If allowed to remain in the study, this will be reported as a major protocol deviation and not a waiver.

The table below lists prohibitions and restrictions by medication class, including representative medications within class. A **prohibited** medication is not allowed. A **restricted** medication is allowed only under certain conditions.

Medication Class	Medication[a]	Prohibition/restrictions
Amyloid beta-directed monoclonal antibodies and other anti-tau therapies	**PROHIBITED** • aducanumab • lecanemab • donanemab	Prohibited from Screening through the end of Visit 6 (EOT/ET) (see also exclusion criterion in Section 4.2)
Antipsychotics	**PROHIBITED** All in class	• Must be completely discontinued by 3 days prior to Baseline (i.e., no antipsychotic dose during the 3 days prior to the day of the Baseline visit) as determined by the Investigator in discussion with the Medical Monitor • Prohibited through the end of Visit 6 (EOT/ET)
Anticholinergics	**PROHIBITED** • benztropine • biperiden • trihexyphenidyl • oral diphenhydramine	• Centrally acting anticholinergic medications must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit. • Long-term or chronic use is prohibited through the end of Visit 6 (EOT/ET)
	RESTRICTED • benztropine • biperiden • trihexyphenidyl • oral diphenhydramine	Short-term use of centrally acting anticholinergics, including anti-allergy medications, is allowed to treat an adverse event.

Medication Class	Medication[a]	Prohibition/restrictions
	UNRESTRICTED • trospium • oxybutynin • topical diphenhydramine	Peripherally acting anticholinergic medications and topical diphenhydramine are allowed without restriction
Anticonvulsant and mood stabilizers	**PROHIBITED** • carbamazepine • lamotrigine • lithium • phenytoin • valproate • gabapentin • pregabalin	• Must be discontinued 5 half-lives prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET) • Valproate, gabapentin, and pregabalin prohibited only when prescribed for the treatment of epilepsy
	RESTRICTED • valproate • gabapentin • pregabalin	Valproate, gabapentin, and pregabalin may be used for the treatment of conditions other than epilepsy if dose unchanged for at least 4 weeks prior to the Baseline visit and expected to remain unchanged until the subject's final visit.
Antidepressants	**PROHIBITED** • mirtazapine • nefazodone • fluvoxamine • mianserin • amitriptyline • nortriptyline • imipramine • trimipramine • desipramine • clomipramine • esketamine • ketamine • trazodone	• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET)
	RESTRICTED • citalopram • escitalopram • venlafaxine • desvenlafaxine (Other SSRI medications such as sertraline are allowed and not restricted.)	• If the subject is remaining on these restricted medications, the dose must be unchanged for at least 4 weeks prior to the Baseline visit and expected to remain unchanged until the subject's final visit. • Desvenlafaxine is restricted to a maximum dose of 50 mg/day. • Citalopram, escitalopram, and venlafaxine can prolong the QT interval and are only allowed under the following conditions: **o** The subject has a Baseline ECG with a QTcF <425 ms IF QRS duration is <120 ms.

Medication Class	Medication[a]	Prohibition/restrictions
		o The subject has a QTcF <450 ms at Baseline IF QRS duration ≥120 ms. o Citalopram is restricted to a maximum dose of 20 mg/day. Escitalopram is restricted to a maximum dose of 20 mg/day. Venlafaxine is restricted to a maximum dose of 225 mg/day.
Anxiolytics	**PROHIBITED** • chlordiazepoxide • diazepam • flurazepam	• Long-acting benzodiazepines must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET)
	RESTRICTED • alprazolam • clonazepam • lorazepam • oxazepam • temazepam • midazolam • triazolam	• Short- or medium-acting benzodiazepine may be used for acute anxiety. Reasonable efforts should be made to use minimum dose necessary for symptom management. • Benzodiazepines (lorazepam up to 1 mg/day or equivalent) are allowed as rescue medication as needed for severe neuropsychiatric or behavioral disturbances. • May not be used within 12 hours prior to an assessment visit
Hypnotics and sleeping agents	**PROHIBITED** • zolpidem • zopiclone • eszopiclone	• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET)
	RESTRICTED • zaleplon • ramelteon	May not be used within 12 hours of a cognitive assessment, and efforts should be made to limit agents to lowest dose for the shortest time needed.
Stimulants and wake-promoting agents	**PROHIBITED** • methylphenidate • modafinil • armodafinil	• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET) (see Section 4.2 and Section 6.3.6 for procedures related to a positive amphetamine test at study entry)
Non-stimulant ADHD medications	**PROHIBITED** • atomoxetine • guanfacine	• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET)
Serotonin antagonists	**PROHIBITED** • cyproheptadine	• Must be discontinued at least 3 weeks prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET)
Antiarrhythmic drugs	**PROHIBITED** • ajmaline • amakalant, semantilide • amiodarone • bretylium	Prohibited from Baseline through the end of Visit 6 (EOT/ET)

Medication Class	Medication[a]	Prohibition/restrictions
	• disopyramide • dofetilide • dronedarone • flecainide • ibutilide • procainamide • propafenone • quinidine • sotalol, d-sotalol	
Opioids	**PROHIBITED** • methadone • buprenorphine	• Must be discontinued at least 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit • Prohibited through the end of Visit 6 (EOT/ET)
Antimicrobials, antifungals, and antimalarials	**PROHIBITED** • clarithromycin • erythromycin • levofloxacin • moxifloxacin • pentamidine • roxithromycin	Prohibited from Baseline through the end of Visit 6 (EOT/ET)
	RESTRICTED • artenimol/piperaquine • azithromycin • bedaquiline • ciprofloxacin • gemifloxacin • norfloxacin • ofloxacin • fluconazole • telavancin • telithromycin	• Prohibited at Baseline but may be used during the course of the study to treat a bacterial infection (e.g., urinary tract infection, respiratory infection), post-Baseline at the discretion of the Investigator • These restricted medications are only allowed under the following conditions: **o** The subject has a Baseline ECG with a QTcF <425 ms IF QRS duration is <120 ms OR **o** The subject has a QTcF <450 ms at Baseline IF QRS duration ≥120 ms.

Abbreviations: ADHD=attention deficit hyperactivity disorder; ECG=electrocardiogram; QRS interval=QRS interval on ECG; QT interval=QT interval on ECG; QTcF=corrected QT interval using Fridericia's correction method

[a] Medications within each class include but are not limited to the examples listed in this table.

Appendix G Prohibited and Restricted Concomitant Medications: Inhibitors and Inducers of Cytochrome P450 3A4 Enzyme

The information presented here is intended to provide guidance and does not constitute an exhaustive list of strong CYP3A4 inhibitors and inducers. Any questions should be discussed with the Medical Monitor or appropriate designee.

Subjects who require current treatment with a prohibited medication will be discontinued from the study.

Subjects who have previously taken a prohibited medication will be discontinued from the study unless:

- the prohibited medication has been discontinued AND
- discontinuation from the study presents an unacceptable medical risk to the subject

The justification to allow the subject to continue in the study will be made by the Sponsor/Medical Monitor with medical input from the Investigator, and will be documented. If allowed to remain in the study, this will be reported as a major protocol deviation and not a waiver.

Studies in human liver microsomes indicate that CYP3A4 is the major CYP enzyme involved in the oxidative metabolism of ACP-204. Consequently, coadministered potent inhibitors or inducers of CYP3A4 will likely increase or decrease, respectively, the plasma concentrations of ACP-204.

Moderate and strong inhibitors of CYP3A4 are to be stopped at least 7 days or 5 half-lives prior to study drug administration, whichever is longer. Moderate and strong inducers of CYP3A4 are to be stopped 30 days or 5 half-lives prior to study drug administration, whichever is longer.

STRONG INHIBITORS	grapefruit juice[a] boceprevir (Victrelis®) clarithromycin (Biaxin®) cobicistat (part of Stribild®) indinavir (Crixivan®) itraconazole (Sporanox®) ketoconazole (Nizoral®) lopinavir and ritonavir (Kaletra®) mibefradil (Posicor®) nefazodone (Serzone®) nelfinavir (Viracept®) posaconazole (Noxafil®) quinupristin (Synercid®) ritonavir (Norvir®, part of Viekira Pak™)	MODERATE INHIBITORS	grapefruit juice[a] amprenavir (Agenerase®) aprepitant (Emend®) atazanavir (Reyataz®) cimetidine (Tagamet®) ciprofloxacin (Cipro®) conivaptan (Vaprisol®) crizotinib cyclosporine darunavir/ritonavir (Prezista®/Ritonavir) diltiazem dronedarone erythromycin (Erythrocin® Lactobionate)

	– combination treatments including ritonavir, such as: danoprevir and ritonavir elvitegravir and ritonavir indinavir and ritonavir lopinavir and ritonavir paritaprevir and ritonavir and ombitasvir (and/or dasabuvir) saquinavir and ritonavir tipranavir and ritonavir saquinavir (Invirase®) telaprevir (Incivek®) telithromycin (Ketek®) troleandomycin voriconazole (Vfend®)		fluconazole (Diflucan®) fluvoxamine (Luvox®) fosamprenavir (Lexiva®) imatinib (Gleevec®) isavuconazole tofisopam verapamil (Calan®)
STRONG INDUCERS	apalutamide avasimibe carbamazepine (Tegretol®) enzalutamide ivosidenib lumacaftor mitotane phenytoin (Dilantin®) rifampin (Rifadin®, Rifadin IV®, Rimactane®) St. John's Wort	MODERATE INDUCERS	bosentan (Tracleer®) cenobamate dabrafenib efavirenz (Sustiva®) etravirine (Intelence®) lorlatinib modafinil (Provigil®) nafcillin (Unipen®, Nallpen®) pexidartinib phenobarbital (Luminal®, Solfoton®) primidone sotorasib

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength). (US FDA Drug Development and Drug Interactions http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit).

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Approval w eSig Task	Peter Zhang Biostatistics 15-Oct-2024 22:04:27 GMT+0000

Approval w eSig Task	Bryan Dirks Clinical 15-Oct-2024 23:04:12 GMT+0000

Approval w eSig Task	Sanjeev Pathak Clinical 15-Oct-2024 23:12:28 GMT+0000

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