Study Design of Phase 2/3, Double-Blind, Placebo-Controlled, Multicenter Trials Investigating the Efficacy and Safety of ACP-204, a Novel 5-HT$_{2A}$ Inverse Agonist/Antagonist, in Alzheimer's Disease Psychosis

Samantha Friend,[1]* Bryan Dirks,[2] Becky Howell,[2] Xiaoshu Feng,[2] Peter Zhang,[2] Sanjeev Pathak[2]

[1]Acadia Pharmaceuticals Inc., San Diego, CA; [2]Acadia Pharmaceuticals Inc., Princeton, NJ

*Presenting author

INTRODUCTION

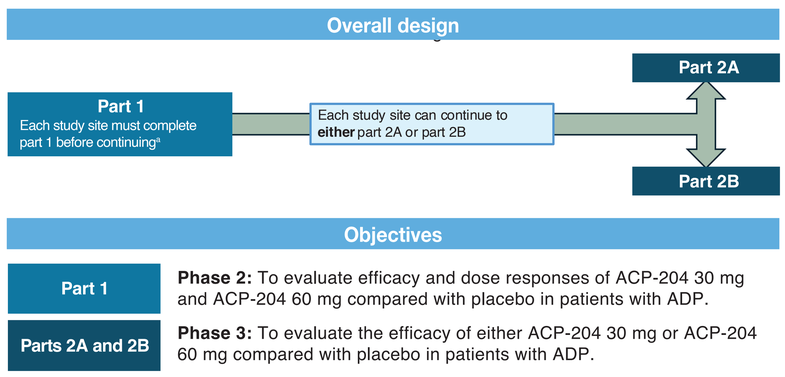
- Psychosis symptoms are characterized by hallucinations and delusions; they are common in various types of dementia, including Alzheimer's disease (AD).[1]
- The prevalences of hallucinations and delusions in AD are 18% and 36%, respectively.[1]
- Atypical antipsychotics are frequently used to treat patients with AD psychosis (ADP) despite serious safety concerns about their use in this vulnerable population.[2]
- Currently, there is no approved pharmacologic treatment for ADP, representing a significant unmet clinical need.
- Pimavanserin, a drug approved to treat hallucinations and delusions in Parkinson's disease psychosis, has been evaluated in treating dementia-related psychoses, including ADP.[3]
- ACP-204 is a novel, highly potent, and selective 5-HT$_{2A}$ inverse agonist/antagonist. It was discovered to have an improved pharmacologic profile compared with its first-in-class analog, pimavanserin.
- While efficacy has not yet been assessed, preliminary data indicate ACP-204 is well tolerated. No safety signals of concern were identified in any of the 3 phase 1 studies.
- Treatment with ACP-204 is being evaluated for efficacy and safety in patients experiencing hallucinations and delusions in ADP.

METHODS

Study Design

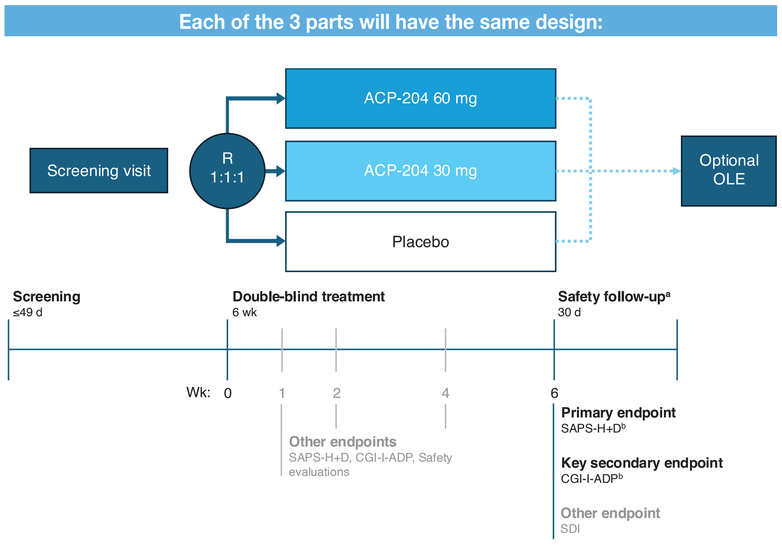
- Study ACP-204-006 (NCT06159673) includes 3 similar, independent, randomized, double-blind, placebo-controlled, multicenter studies ("parts") investigating the efficacy and safety of ACP-204 in patients with ADP (**Figure 1**).[4]
  - Part 1: a phase 2 proof-of-concept and dose-finding study
  - Parts 2A and 2B: a phase 3 confirmatory efficacy study
- Each of the 3 parts will include a ≤49 day screening period, 6-week double-blind treatment period, and 30-day safety follow-up period (**Figure 2**).
- This ongoing study has an estimated completion date of February 2028.
- The full analysis set includes all randomized participants who received ≥1 dose of the study drug and who have both a baseline value and ≥1 postbaseline value for the Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions (SAPS-H+D).
- The safety analysis set includes all randomized participants who received ≥1 dose of the study drug.
- The per-protocol analysis set will consist of those participants in the full analysis set without any protocol deviations that could have a substantial effect on the primary outcome.

Figure 1. Overall Design and Objectives of the 3 Studies



ADP, Alzheimer's disease psychosis.
[a]Study participants can only participate in 1 part of the study.

Figure 2. Study Design Schematic



CGI-I-ADP, Clinical Global Impression–Improvement in Alzheimer's Disease Psychosis; OLE, open-label extension; SAPS-H+D, Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions; SDI, Sleep Disorders Inventory; R, randomized.
[a]Participants who enroll in the optional OLE will not participate in the 30-day safety follow-up period of this study. Safety follow-up consists of 2 telephone calls at 7 (±3) days and 30 (+4) days after the last dose of the study drug. Participants who discontinue the study early will receive a mortality follow-up phone call 30 (+4) days after the last dose of the study drug.
[b]Change from baseline.

Study Participants

- Eligible participants (**Table 1**) in each study will be randomized 1:1:1 to receive ACP-204 60 mg, ACP-204 30 mg, or placebo in the 6-week double-blind treatment period.
  - Participants who complete parts 1, 2A, or 2B may be eligible to roll over into a long-term open-label extension study, ACP-204-008 (NCT06194799).[5]

Table 1. Select Eligibility Criteria

Inclusion criteria	Exclusion criteria
• Aged 55-95 y (inclusive) • Diagnosis of probable AD, defined by NIA-AA 2011 criteria • Presence of AD-related biomarker[a] • MRI or CT scan findings consistent with AD diagnosis • Meets revised IPA criteria for psychosis in NCDs • Presence of psychosis symptoms for ≥2 mo prior to screening visit • The following scores at screening and baseline: – MMSE score of ≥6 and ≤24 – NPI or NPI-NH hallucinations score of ≥6, delusions score of ≥6, or psychosis score[b] of ≥9 – CGI-I-ADP score of ≥4 • Has a designated study partner/caregiver who can accurately report participant's symptoms	• In hospice and receiving end-of-life palliative care or has become bedridden • Requires skilled nursing care[c] • Psychotic symptoms are primarily attributable to delirium, substance abuse, or a medical or psychiatric condition other than dementia • MDE meeting *DSM-5* criteria within 3 mo of screening • Actively suicidal[d] • Evidence of a nonneurologic medical comorbidity or medication use that could substantially impair cognition • Known personal or family history or symptoms of long QT syndrome • History of nonresponse to pimavanserin treatment

AD, Alzheimer's disease; C-SSRS, Columbia–Suicide Severity Rating Scale; CGI-I-ADP, Clinical Global Impression–Improvement in Alzheimer's Disease Psychosis; CSF, cerebrospinal fluid; CT, computed tomography; *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; GCAS, Global Clinician Assessment of Suicidality; IPA, International Psychogeriatrics Association; MDE, manic depressive episode; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NCD, neurocognitive disorder; NIA-AA, National Institute on Aging–Alzheimer's Association; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory–Nursing Home Version; PET, positron emission tomography.
[a]At screening assessment or historical; includes blood-based biomarkers, PET scan, CSF biomarkers of neuropathologic change consistent with AD.[6]
[b]Psychosis score = hallucinations plus delusions domains scores.
[c]Procedures that can only be administered by a registered nurse or doctor.
[d]At screening or baseline; includes including an answer of "yes" to C-SSRS questions 4 or 5 (current or over the last 6 months), has attempted suicide in the 2 years prior to screening, or has a GCAS score of 3 or 4 within 3 months of screening.

- For patients taking a cholinesterase inhibitor, memantine, or both, the following must apply:
  - The dose must be stable for ≥12 weeks prior to baseline.
  - If discontinued, the discontinuation must have occurred ≥2 weeks prior to baseline.
- For patients taking an antipsychotic at screening, the medication must be discontinued ≥3 days prior to baseline.
  - Discontinuation cannot be for the sole purpose of study enrollment.

Table 2. Study Endpoints

Endpoints		
Primary • Change from baseline to week 6 in the SAPS-H+D total score **Key Secondary** • CGI-I-ADP score at week 6	**Select Other** • CGI-I-ADP score at weeks 1, 2, and 4 • Change from baseline as follows: – SAPS-H+D total score at weeks 1, 2, and 4 – Sleep Disorders Inventory score at week 6	**Safety** • TEAEs • Electrocardiograms • Vital signs and clinical/laboratory examinations • Suicidality as measured by the following: – Global Clinician Assessment of Suicidality score – Columbia–Suicide Severity Rating Scale • Udvalg for kliniske undersøgelser Sleepiness/Sedation and Orthostatic Dizziness scores • Mini-Mental State Examination score • Extrapyramidal Symptom Rating Scale–Abbreviated scores

CGI-I-ADP, Clinical Global Impression–Improvement in Alzheimer's Disease Psychosis; SAPS-H+D, Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions; TEAE, treatment-emergent adverse event

- Benzodiazepines are allowed as rescue medication as needed for severe neuropsychiatric or behavioral disturbances. Benzodiazepine rescue medication, lorazepam ≤1 mg/d, or equivalent may be prescribed.
- Part 1 of the study will enroll ~318 participants (~106/arm), and parts 2A and 2B will each enroll ~378 participants (~126/arm), providing ≥80% (part 1) or ≥85% (part 2A and 2B) power to detect a significant effect of ACP-204 over placebo at alpha level 0.05 using a 2-sided test.
- All 3 study parts (part 1, part 2A, and part 2B) will be analyzed separately from each other.
- The primary endpoint (**Table 2**), which is the change from baseline in SAPS-H+D total score, will be analyzed using the mixed-effect model repeated measures with effects for treatment groups, visit, treatment-by visit interaction, baseline SAPS-H+D total score-by-visit interaction, and factors for stratifying randomization (eg, site and institution status).
- 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 (2-sided) using the full analysis set of each part. The difference in the least squares means, corresponding 95% confidence interval, and *P* value will be reported.
- The key secondary efficacy endpoint, which is the CGI-I-ADP score at week 6, will be analyzed in a similar fashion as the primary endpoint.
- Safety results will be summarized by treatment group using descriptive statistics.

CONCLUSIONS

- This is a randomized, double-blind, placebo-controlled, multicenter trial for patients with ADP, a condition with no pharmacologic treatment approved by the US Food and Drug Administration.
- The results from this trial will characterize the efficacy and safety of ACP-204 in patients with ADP.

ACKNOWLEDGMENTS

These studies are being funded by Acadia Pharmaceuticals. Medical writing support was provided by Citrus Scientific, a Citrus Health Group, Inc., company (Chicago, Illinois), and was funded by Acadia Pharmaceuticals in accordance with GPP 2022 Guidelines.

DISCLOSURES

SF, **BD**, **BH**, **XF**, **PZ**, and **SP** are employees of Acadia Pharmaceuticals, Inc., and may own stock and/or stock options.

REFERENCES

1. Jellinger KA. *J Cell Mol Med*. 2012;16(5):995-1012.
2. Schneider LS, et al. *N Engl J Med*. 2006;355(15):1525-1538.
3. Tariot PN, et al. *N Engl J Med*. 2021;385(4):309-319.
4. ClinicalTrials.gov. ACP-204 in Adults With Alzheimer's Disease Psychosis. 2025. https://clinicaltrials.gov/study/NCT06159673
5. ClinicalTrials.gov. ACP-204 in Adults With Alzheimer's Disease Psychosis Open Label Extension Study. 2025. https://clinicaltrials.gov/study/NCT06194799
6. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14(4):535-562.

Presented at the American Association for Geriatric Psychiatry 2025 Annual Meeting; March 14-17, 2025; Phoenix, AZ

ACADIA