ACADIA®

acadia
medical affairs

Acadia Pharmaceuticals Inc. is providing this letter in response to your unsolicited request for medical information. It is for scientific exchange and individual educational purposes only, and should not be copied or distributed.

ACP-204 is an investigational agent, and its safety and efficacy have not been established and approved by the FDA. This letter is not intended to promote or recommend ACP-204 for any use. Acadia strives to provide current, accurate, and fair-balanced information in compliance with current industry information dissemination guidelines.

12830 El Camino Real · Suite 400 · San Diego, California 92130 · USA · Tel. 858.558.2871 · Fax 858.558.2872 · www.acadia-pharm.com

ACP-204 Clinical Development Program in Alzheimer's Disease Psychosis

This letter is provided in response to your specific request for information regarding the ACP-204 clinical development program in Alzheimer's disease (AD) psychosis. ACP-204 is an investigational agent, and its safety and efficacy for the treatment of hallucinations and delusions associated with AD psychosis have not been established and approved by the FDA.

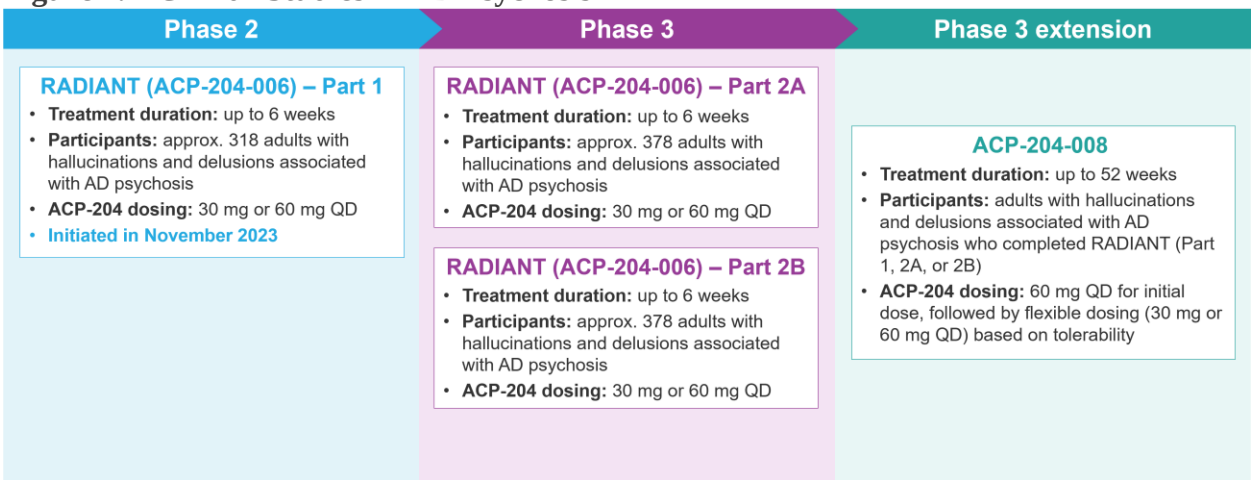
Summary

- The efficacy and safety of ACP-204 (30 mg and 60 mg, once daily [QD]) is being investigated in adults with hallucinations and delusions associated with AD psychosis in the RADIANT study (**ACP-204-006**), which comprises three parts: one Phase 2 substudy (enrolling approximately 318 participants) and two Phase 3 substudies (enrolling approximately 378 participants).[1]
    - The primary endpoint for each substudy is the change from baseline in Scale for the Assessment of Positive Symptoms, Hallucinations and Delusions subscales (SAPS-H+D) total score at Week 6.[1]
- Participants completing any of the RADIANT substudies will be eligible to enroll in an open-label extension (OLE) study, **ACP-204-008**, that will evaluate the safety and tolerability of long-term ACP-204 treatment in participants with AD psychosis for up to 52 weeks.[1,2]

Clinical Studies in AD Psychosis

The efficacy and safety of ACP-204 is being investigated in participants with hallucinations and delusions associated with AD psychosis in the three-part RADIANT study, which comprises three independent substudies of 6 weeks duration, and a long-term OLE study (**Figure 1**).[1,2]

Figure 1. ACP-204 Studies in AD Psychosis[1,3]



Abbreviations: AD=Alzheimer's disease; QD=once daily.

RADIANT (ACP-204-006)

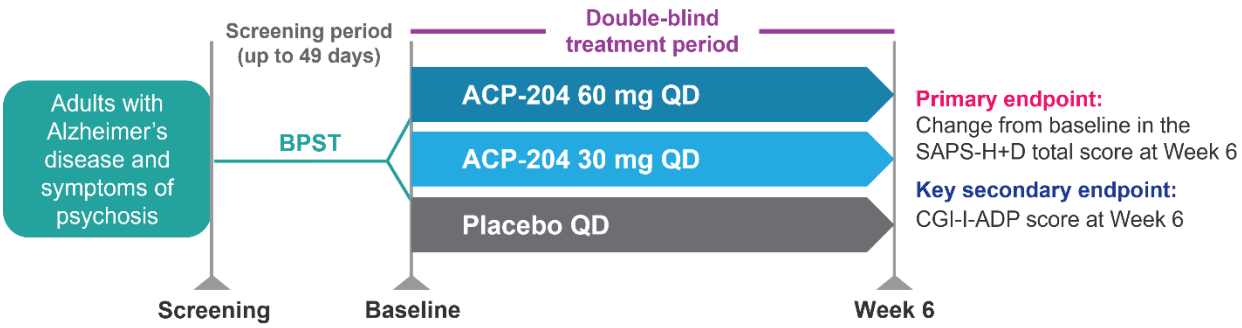
ACP-204-006 is a master protocol for three independent, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2/3 substudies in participants with AD psychosis. Participants will be enrolled into either Part 1 (Phase 2 substudy, estimated 318 participants), which will evaluate efficacy and dose response of ACP-204 60 mg QD and ACP-204 30 mg QD compared with placebo in participants with AD psychosis, or Part 2A or Part 2B (Phase 3 substudies, estimated 378 participants each), which will be confirmatory of either both doses or only a single dose from Part 1. Participants may be enrolled into only one substudy.[1,4]

The primary efficacy objective for each substudy is as follows:[1]

- Part 1: to evaluate efficacy and dose response of ACP-204 60 mg and ACP-204 30 mg compared with placebo in participants with AD psychosis as measured by the 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 participants with AD psychosis as measured by SAPS-H+D total score.

The design for each substudy in RADIANT is shown in **Figure 2**. For each substudy there will be a screening period of up to 49 days,[1] during which the designated study partner/caregiver will be given instructions on engaging in a structured psychosocial interaction with the participant (brief psychosocial therapy).[5]

Figure 2. RADIANT Study Design (Part 1, Part 2A and Part 2B)[1,5]



Abbreviations: ADP=Alzheimer's disease psychosis; BPST=brief psychosocial therapy; CGI-I-ADP=Clinical Global Impression–Improvement in the ADP context; QD=once daily; SAPS-H+D=Scale for the Assessment of Positive Symptoms, Hallucinations and Delusions subscales.

After completing the 6-week double-blind treatment period, participants from each substudy who do not enroll in the OLE study will undergo a 30-day safety follow-up period. An additional mortality follow-up will be conducted for participants who discontinue prematurely from the study 30 days after the participant's intended day of last dose of study drug.[1] Selected inclusion and exclusion criteria for each substudy in RADIANT are shown in **Table 1**.

Table 1. RADIANT Selected Inclusion and Exclusion Criteria[1,4]

Selected inclusion criteria

• Male or female participants, ≥55 and ≤95 years of age living in the community or in an institutionalized setting
• Meets clinical criteria for possible or probable AD based on 2011 NIA-AA criteria
• Has either blood-based biomarker OR documented evidence indicating amyloid plaque deposition and neuropathologic change consistent with AD
• Meets the revised criteria for psychosis in major or mild neurocognitive disorder established by the IPA
• MMSE score ≥6 and ≤24 at screening and baseline
• Had psychotic symptoms for ≥2 months prior to screening visit
• Has the following scores at screening and baseline:
  ○ NPI or NPI-NH Hallucinations Domain score ≥6 or Delusions Domain score ≥6 or Psychosis score (Hallucinations plus Delusions Domains scores) ≥9, AND
  ○ CGI-S-ADP score ≥4
• Has a prior MRI or CT scan of the brain that is consistent with the diagnosis of AD
• Must be on a stable dose of cholinesterase inhibitor or memantine, if applicable

Selected exclusion criteria
• In hospice and receiving end-of-life palliative care, or has become bedridden • Requires ongoing skilled nursing or medical care of IV lines or surgical openings to the wind-pipe or bladder • Has psychotic symptoms that are primarily attributable to delirium, substance abuse, or a medical or psychiatric condition other than dementia • Has evidence of a non-neurologic medical comorbidity or medication use that could substantially impair cognition • Has a known history of cerebral amyloid angiopathy, epilepsy, central nervous system neoplasm, or unexplained syncope • Atrial fibrillation • Symptomatic orthostatic hypotension • Has a known personal or family history or symptoms of long QT syndrome

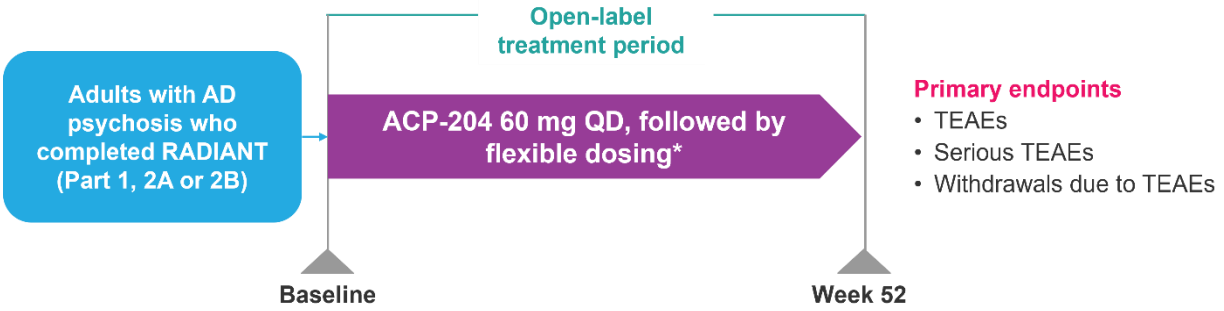
Abbreviations: AD=Alzheimer's disease; ADP=Alzheimer's disease psychosis; CGI-S-ADP=Clinical Global Impression-Severity in the ADP context; CT=computed tomography; IPA=International Psychogeriatrics Association; IV=intravenous; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NIA-AA=National Institute on Aging-Alzheimer Association; NPI=Neuropsychiatric Inventory; NPI-NH=Neuropsychiatric Inventory–Nursing Home Version.

All three substudies will be analyzed independently of each other. The Phase 2 substudy, RADIANT Part 1, was initiated in November 2023.[4]

ACP-204-008

This is a 52-week OLE study enrolling participants who completed Part 1, 2A or 2B of the RADIANT study (**Figure 3**). The primary objective is to evaluate the safety and tolerability of long-term ACP-204 treatment in participants with AD psychosis.[2]

Figure 3. Study Design for ACP-204-008[3]



**After the initial ACP-204 dose of 60 mg on the day after the baseline visit, the ACP-204 dose may be adjusted first down for tolerability concerns or later up for suboptimal efficacy, once or more than once, to 30 mg or 60 mg administered QD.*
Abbreviations: AD=Alzheimer's disease; QD=once daily; TEAE=treatment-emergent adverse event.

All eligible rollover participants from RADIANT will begin ACP-204 60 mg QD dosing on the day after the end-of-treatment visit for the antecedent study, which serves also as the baseline visit for this study, ACP-204-008. After the initial ACP-204 dose of 60 mg on the day after the baseline visit, the ACP-204 dose is flexible, and may be adjusted first down for tolerability concerns or later up for suboptimal efficacy, once or more than once, to 30 mg or 60 mg administered QD.[3]

References

1. Friend S, et al. Study Design of Phase 2/3, Double-Blind, Placebo-Controlled, Multicenter Trials Investigating the Efficacy and Safety of ACP-204, a Novel 5-HT2A Inverse Agonist/Antagonist, in Alzheimer's Disease Psychosis. Poster presented at the American Association for Geriatric Psychiatry 2025 Annual Meeting; March 14-17, 2025.
2. National Institutes of Health. ACP-204 in Adults With Alzheimer's Disease Psychosis Open Label Extension Study. **[Link]**.
3. Acadia Pharmaceuticals Inc. Data on File. ACP-204-008 Protocol. 2023.
4. National Institutes of Health. ACP-204 in Adults With Alzheimer's Disease Psychosis. **[Link]**.
5. Acadia Pharmaceuticals Inc. Data on File. ACP-204-006 Protocol. 2023.