An innovative clinical trial designed to evaluate the effects of ACI-24.060 in Alzheimer's Disease (AD) and in Down syndrome (DS) - (ABATE Study)

P1-735

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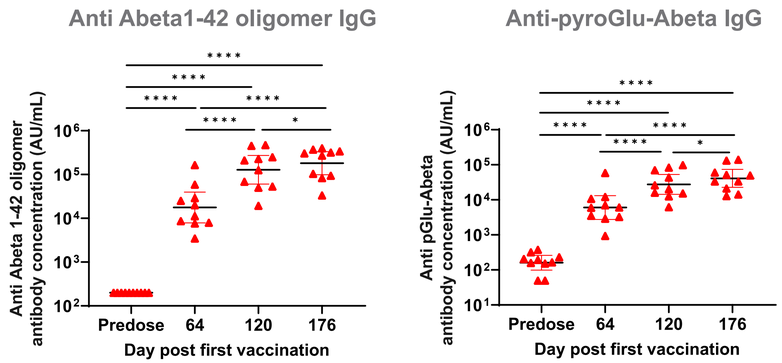
Background

Sporadic Alzheimer's disease (AD) and Down syndrome-related AD (DSAD) share a common neuropathologic picture, with hallmark amyloid plaques and neurofibrillary tangles. The key constituents, amyloid beta (Abeta) and Tau, respectively, define the biomarker picture shared between sporadic AD, DSAD and autosomal dominant AD. Small Abeta oligomers and pyroglutamate Abeta3-42 (pGlu-Abeta3-42) are key for disease initiation and neurotoxicity. ACI-24 is an active immunotherapy targeting Abeta which significantly reduces Abeta plaque burden in a preclinical model. Initial clinical data demonstrated safety and pharmacodynamic response, both in sporadic AD and people with DS. Preclinical data recently demonstrated that a new, optimized formulation of ACI-24 (ACI-24.060) has significantly improved immunogenicity against key toxic species, i.e., Abeta oligomers and pGlu-Abeta3-42.

The ABATE study's (NCT05462106) innovative translational clinical trial design evaluates the effects of ACI-24.060 in sporadic AD (Part 1) and in people with DS (Part 2). The biomarker-based design with multiple interim analyses, enables **(I)** an early assessment of safety and immunogenicity, **(II)** an appropriate dose selection using readouts on translational biomarkers including amyloid PET, **(III)** the safe transition into the DS population and **(IV)** an informed transition into pivotal studies. The use of these shared biomarkers in predictable and pre-specified trajectories allows effective cross-learnings between sporadic AD and DSAD and has been enabled by the recent results with anti-Abeta monoclonal antibodies, strongly enabling this translational approach for an amyloid immunotherapy.

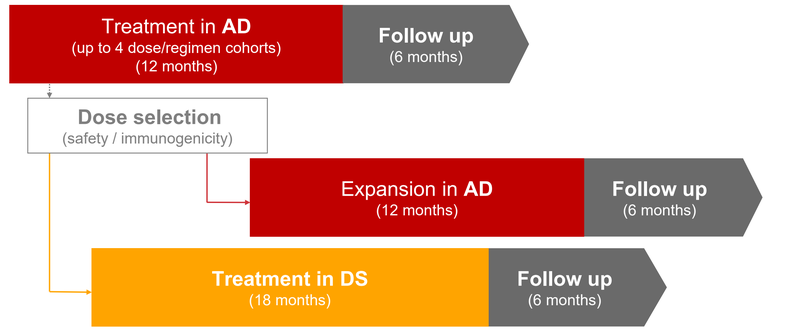
ACI-24.060 generates a strong antibody response against Abeta oligomers and pyroglutamate Abeta in NHP



* p<0.05 **** p<0.0001 - Injections on days 0, 29, 57, 85, 113, 141, 169

ACI-24.060 targets the highly toxic species of Abeta and induces strong, boostable, homogeneous IgG titers in non-human primates (NHP).

Biomarker-based, adaptive trial design – ABATE study



Both
- Interim analyses of safety/tolerability & immunogenicity
- Biomarker analyses including Abeta PET and others

AD
- Up to 4 different doses and/or dose regimens
- Expansion of one cohort to assess effect on Abeta PET

DS
- Initiation using selected dose identified in AD
- (based on safety/tolerability and immunogenicity)

Multiple interim analyses, enabling early, informed decision-making and multiple opportunities for acceleration:

- expansion of the study
- initiation of pivotal trials, and/or
- initiation of prevention trials

Current study status

Two cohorts assessing two different doses of ACI-24.060 in subjects with prodromal AD are currently ongoing. Anti-Abeta antibody response has been observed in interim findings. No particular safety concerns, and notably no case of ARIA-E at brain MRI, have been observed in the study to date.

The dosing in the study population with DS has been initiated based on the immunogenic and safe dose observed in the prodromal AD study population.

Further safety and immunogenicity findings from both ABATE cohorts are expected in H2 2023. Initial data on amyloid plaque reduction measured via PET imaging are anticipated in H1 2024.

Study population – key selection criteria

Prodromal AD	DS
Male and female	
PET scan at screening consistent with the presence of amyloid pathology	
▪ ≥50 and ≤85 years	▪ ≥35 and ≤50
▪ Diagnosis of prodromal AD: MCI due to AD according to National Institute on Aging Alzheimer's Association (NIA-AA) criteria. ▪ Clinical Dementia Rating (CDR)-Global Score of 0.5. ▪ Subjects either not taking any marketed treatment for AD or receiving a stable dose of an acetylcholinesterase inhibitor (ACHEI) and/or memantine for at least 2 months prior to baseline.	▪ Cytogenetic diagnosis being either trisomy 21 or complete unbalanced translocation of the chromosome 21. ▪ Mild to moderate intellectual disability as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification. ▪ No clinical diagnosis of AD dementia as per International Classification of Diseases 10 (ICD-10).

Main study outcomes

Prodromal AD subjects:
- Primary: Safety and tolerability of ACI-24.060.
- Secondary: Aβ antibody response generated in serum.
- Exploratory: Effect on amyloid-PET scan, on other biomarkers including Tau-PET and biofluid biomarkers, on behavior, cognition, and clinical function.

Subjects with DS:
- Primary: Safety and tolerability of ACI-24.060, Aβ antibody response generated in serum.
- Secondary: Effect on amyloid PET-scan, on amyloid-related biomarker.
- Exploratory: Effect on other biomarkers including Tau-PET and biofluid biomarkers, on behavior, cognition, and clinical function.

Conclusion

- The ongoing ABATE study is the first study evaluating the effects of an active anti-amyloid immunotherapy in two study populations, i.e., subjects with prodromal AD and subjects with Down syndrome.
- The main objectives will be to establish the effects of ACI-24.060 on safety/tolerability, immunogenicity and plaque clearance with amyloid-PET scan in these two study populations.
- The study design will allow an early and de-risked decision on subsequent clinical development and accelerated entry into the pivotal stage.
- FDA has granted a Fast Track designation for ACI-24.060 for the treatment of Alzheimer's disease (AD) in June 2023.

