ACI-35.030 anti-phospho-Tau active immunotherapy for the treatment of early Alzheimer's Disease (AD): Update from the Phase 1b/2a study data and perspectives.

LP031

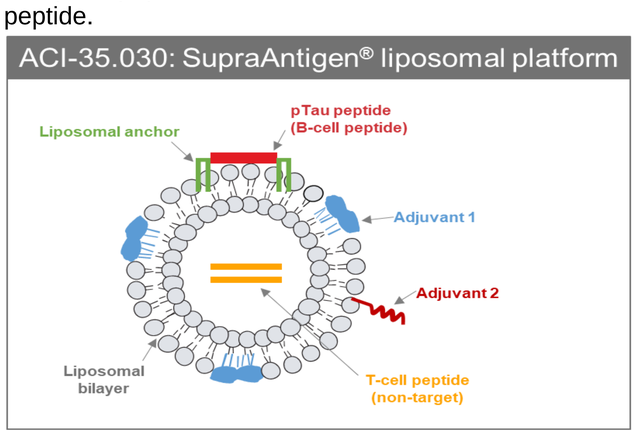
Olivier Sol[1], Johannes Streffer[2], Julien Mermoud[1], Marija Vukicevic[1], Eva Gollwitzer[1], David Hickman[1], Valérie Hliva[1], Julian Gray[1], Lennert Steukers[3], Lingjue Li[4], Andrea Pfeifer[1], Marie Kosco-Vilbois[1], Philip Scheltens[5]
[1]AC Immune SA - Lausanne (Switzerland), [2]University of Antwerp – Antwerp (Belgium), [3]J&J Innovative Medicine (Belgium), [4]J&J Innovative Medicine (United States), [5]Alzheimer Center Amsterdam, Neurology, Vrije Universiteit, Amsterdam, VUmc - Amsterdam (Netherlands)

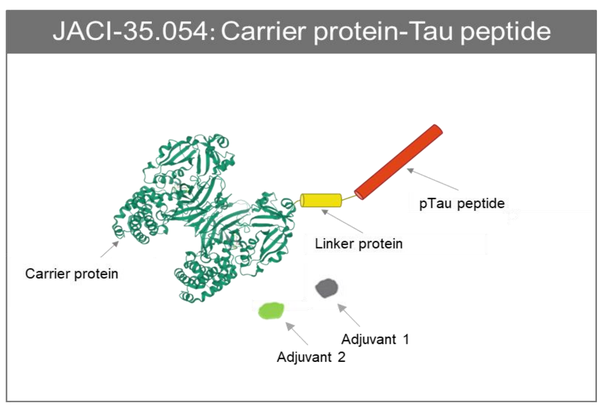
Background:

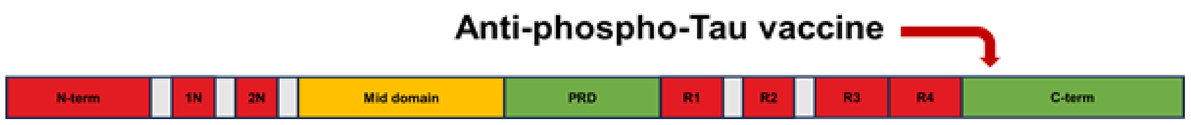
Two active immunotherapies, ACI-35.030 (liposomal formulation) and JACI-35.054 (conjugated formulation), targeting phosphorylated-Tau (pTau) are currently being tested in a Phase 1b/2a clinical trial (NCT04445831) to evaluate the safety, tolerability and immunogenicity of different doses of these clinical candidates.
Following data presented at CTAD in 2022, confirming the strong and specific antibody response profile of ACI-35.030, including maturation of the patient's antibodies towards pathological Tau, this candidate was selected for further development in collaboration with J&J Innovative Medicine. We present here the latest available interim data from the study that is still blinded. This includes data not yet reported elsewhere, including immunogenicity data for ACI-35.030 up to week 50 (expanded sub-cohort 1.2) and up to week 74 (sub-cohort 1.3) and for JACI-35.054, up to week 50 (sub-cohort 2.2), along with an update on safety and tolerability.

Structure of ACI-35.030 and of JACI-35.054:

The pTau peptide is identical in the two active immunotherapies and is directed toward the C-terminal end of the peptide.

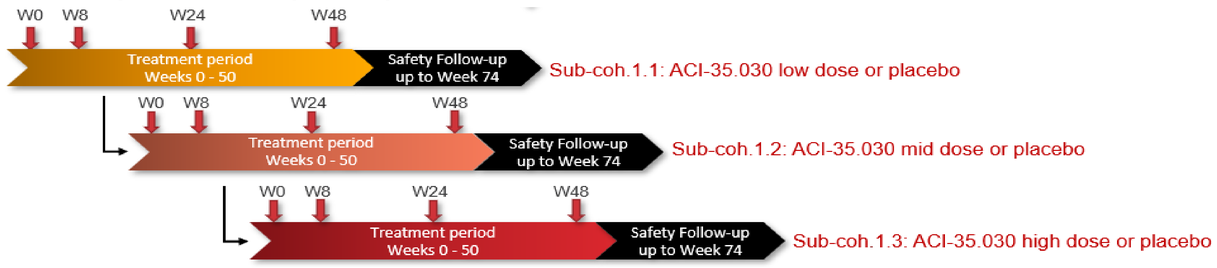




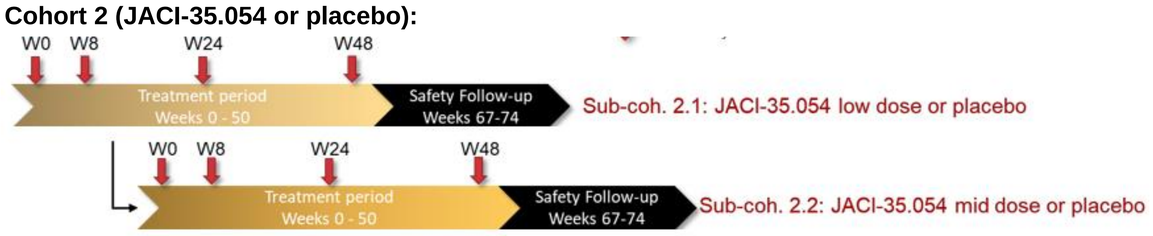


Overall study design:

Cohort 1 (ACI-35.030 or placebo):



Cohort 2 (JACI-35.054 or placebo):



Study population – key selection criteria :

- Male or female with age from 50 and up to 75 years old inclusive.
- Mild Cognitive Impairment (MCI) due to AD or Mild AD according to NIA-AA criteria.
- Clinical Dementia Rating scale (CDR) global score of 0.5 or 1.
- Mini Mental State Examination (MMSE) score of 22 or above.
- Decreased level of CSF Abeta 42 consistent with AD pathology.

Main study outcomes:

Primary:

- Safety and tolerability of active immunotherapies
- Immunogenicity of active immunotherapies (induction of IgG titers against phosphorylated Tau (ie., ePHF and pTau) in serum)

Secondary:

- Immunogenicity of active immunotherapies (induction of IgG titers against Tau and IgM titers against pTau and Tau in serum)

Exploratory:

- Effect of active immunotherapies on putative biomarkers of the progression of AD
- Effect of active immunotherapies on behavior, cognitive and functional performance

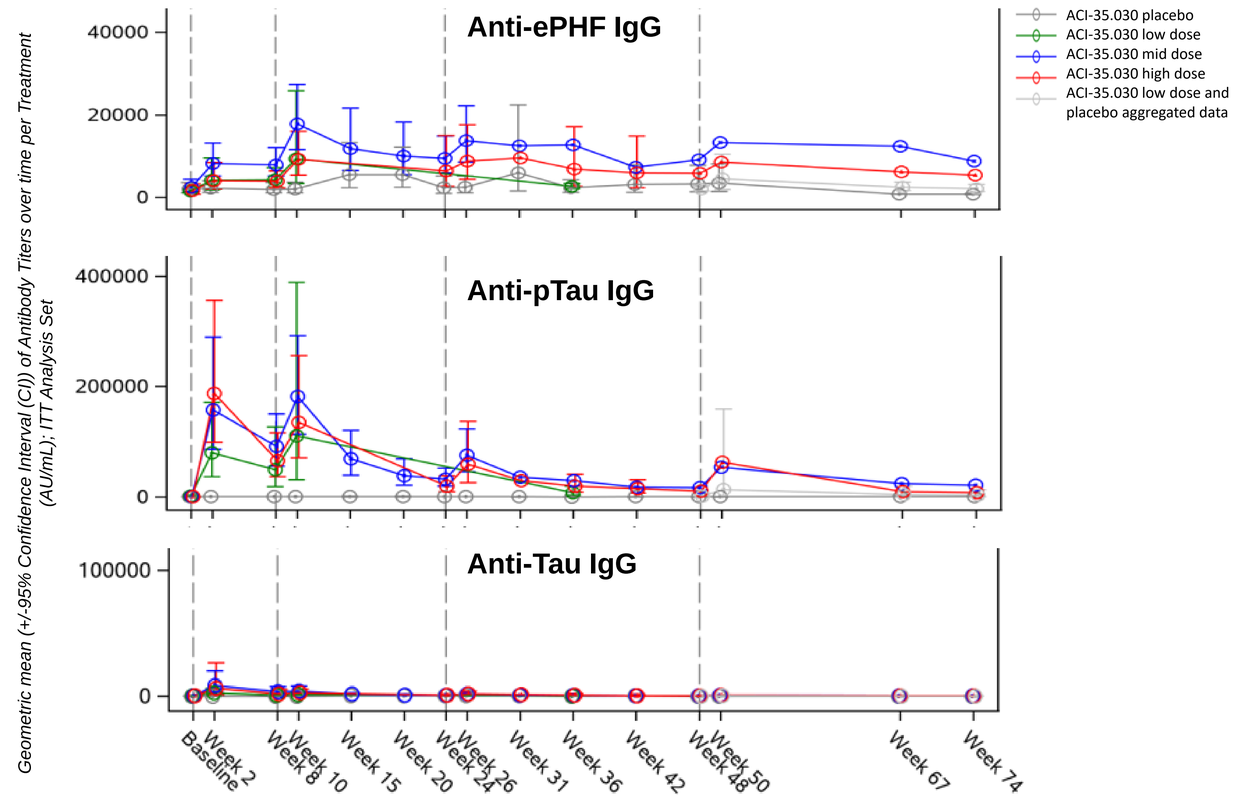
Study demographics:

	Sub-cohort 1.1 (N=8)	Sub-cohort 1.2 (N=25)	Sub-cohort 1.3 (N=8)	Sub-cohort 2.1 (N=8)	Sub-cohort 2.2 (N=8)	Total (N=57)
Sex (F/M)	**5/3**	**11/14**	**4/4**	**5/3**	**5/3**	**30/27**
Age (Years) (Range)	**65.25** (61 - 75)	**68.36** (51 - 75)	**64.88** (56 - 71)	**67.13** (56 - 73)	**64.13** (58 - 75)	**66.67** (51 - 75)
CDR-SB (Mean) (Range)	**2.75** (1 - 5)	**2.46** (0.5 – 5.5)	**2.44** (1 – 4.5)	**3.00** (1.5 – 5.5)	**2.44** (0.5 - 5)	**2.57** (0.5 – 5.5)
MMSE (Mean) (Range)	**26.25** (22 - 29)	**26.16** (22 - 30)	**26.75** (23 - 30)	**26.75** (22 - 30)	**25.75** (22 - 30)	**26.28** (22 - 30)

Interim study results:

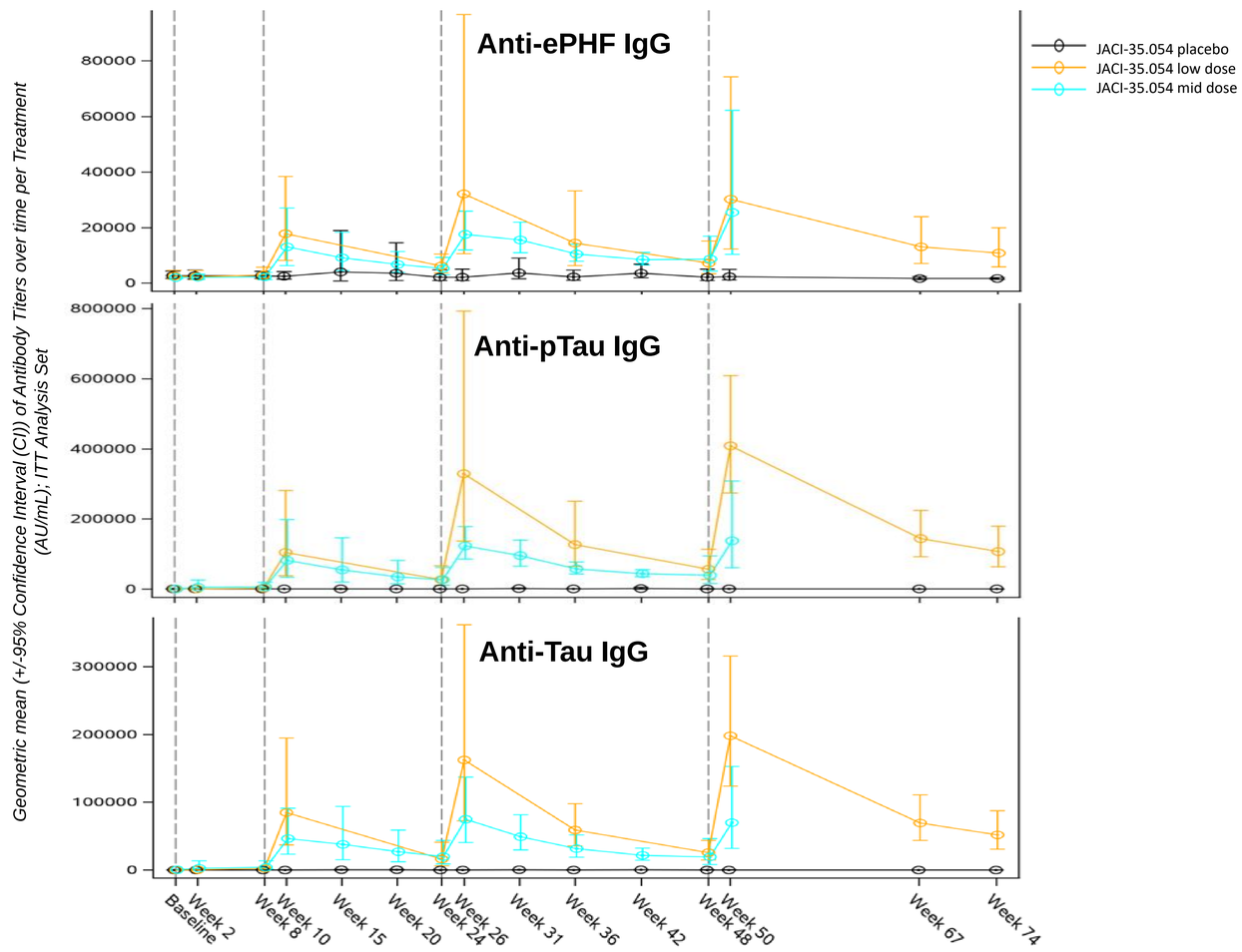
Antibody response of ACI-35.030:

An early response (as soon as 2 weeks after the first injection) and a high responder rate were observed with ACI-35.030. A strong, boostable and durable IgG antibody response was observed against pTau and enriched paired helical filaments (ePHF) demonstrating a specific response profile of ACI-35.030 directed against pathological forms of Tau.



Antibody response of JACI-35.054:

JACI-35.054 showed good, although lower, responder rates with a kinetic profile showing a delayed onset of antibody response. The antibody titers exhibited generally a higher variability, a lower specificity for pathological Tau species and a preference for only the C terminal of the immunogenic peptide.



Safety/tolerability:

Safety and tolerability have been good in the study. There have been no withdrawals due to adverse events. No deaths have occurred. Nine serious adverse events (SAE) have been recorded with ACI-35.030 or placebo, of which 7 were considered unlikely related to study drug and 2 (injection site rash and dizziness in the same participant) were considered probably and possibly related to study drug respectively. One SAE, considered unlikely related to study drug, was reported in a participant receiving JACI-35.054 or placebo. The commonest adverse events have been injection site reactions, observed in approximately half of participants on one or more occasions to date and have been mild to moderate in all but one case. There have been no clinically significant new lesions on MRI scans to date. Two microhemorrhages were detected for the first time at the end of the 6-month safety follow-up visit in one participant receiving ACI-35.030 or placebo in sub-cohort 1.2. There have been no clinically significant changes or abnormalities in vital signs, ECGs, CSF, hematology or biochemistry parameters that were considered to be related to the study drug.

Conclusion: In general, the liposome-based active immunotherapy ACI-35.030 showed a robust antibody profile in terms of rapid response, high responder rate, homogeneity of the antibody response across study participants, epitope coverage and evidence of antibody maturation towards pathologic forms of Tau.
ACI-35.030 has been selected to move into the next stage of clinical development in preclinical AD.