ACI-35.030 and JACI-35.054, two novel anti-phospho-Tau vaccines for the treatment of Alzheimer's Disease: Interim Phase 1b/2a data on safety, tolerability and immunogenicity

Johannes Streffer[1,2], Julien Mermoud[1], Olivier Sol[1], Marija Vukicevic[1], Emma Fiorini[1], Eva Gollwitzer[1], Valérie Hliva[1], David Hickman[1], Julian Gray[1], Piergiorgio Donati[1], Maria Pilar Lopez Deber[1], Julien Rongère[1], Andrea Pfeifer[1], Marie Kosco-Vilbois[1], Philip Scheltens[3,4]

1) AC Immune SA, Lausanne, Switzerland
2) University of Antwerp, Belgium
3) Alzheimer Center Amsterdam, The Netherlands
4) EQT Life Sciences Amsterdam The Netherlands

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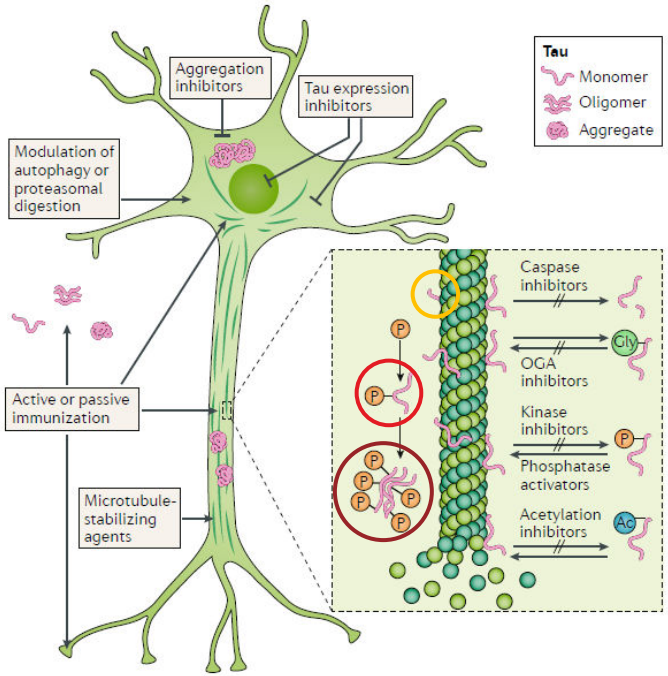
Conflict of interest disclosure

Johannes Streffer is an employee of AC Immune entitled to stock options.

Active immunization for early intervention in Alzheimer's Disease

Preventing Tau spreading and disease progression

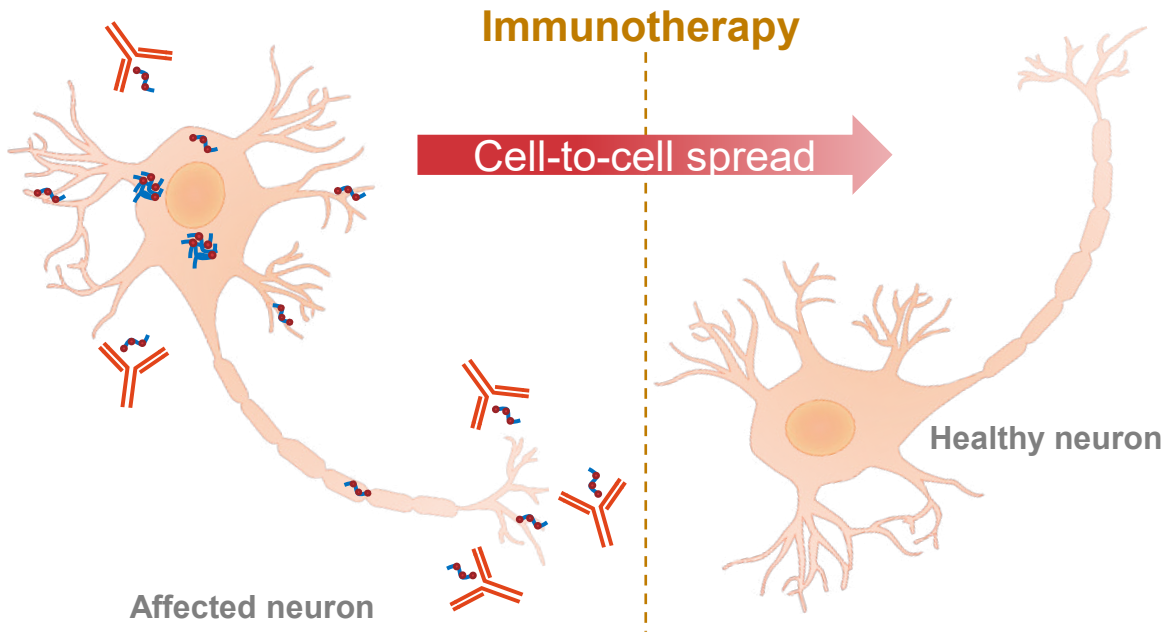
Hyperphosphorylated Tau aggregates in Alzheimer's disease



Congdon et al., Nature Reviews Neurology, 2018

Study measures antibodies against:

- Non-phosphorylated Tau protein
- Phosphorylated Tau protein
- Enriched Paired Helical Filaments (ePHF)



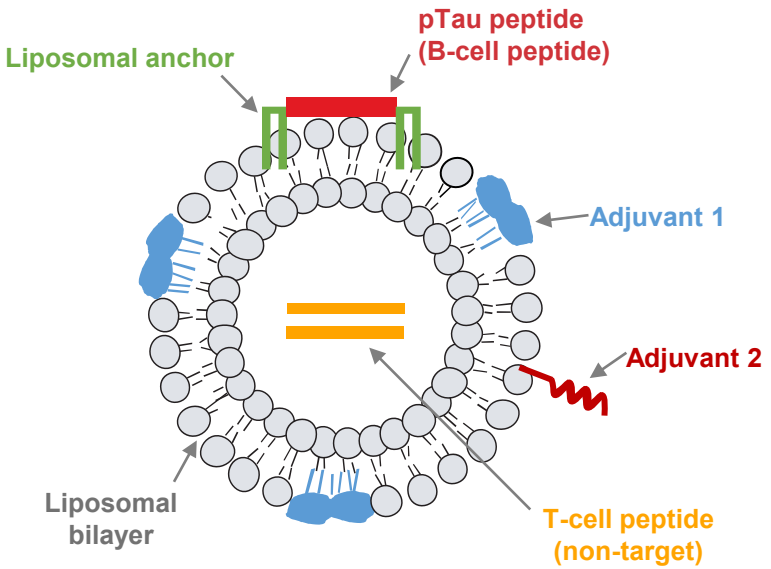
- Targeting Tau is well validated by neuro-pathology and pre-clinical results
- Antibodies are suggested to selectively bind, trap and remove pathological Tau species to prevent cell-to-cell spread

- ACI-35.030 induces antibodies targeting the toxic forms of Tau (pTau and ePHF) to prevent spreading of the pathology from cell-to-cell

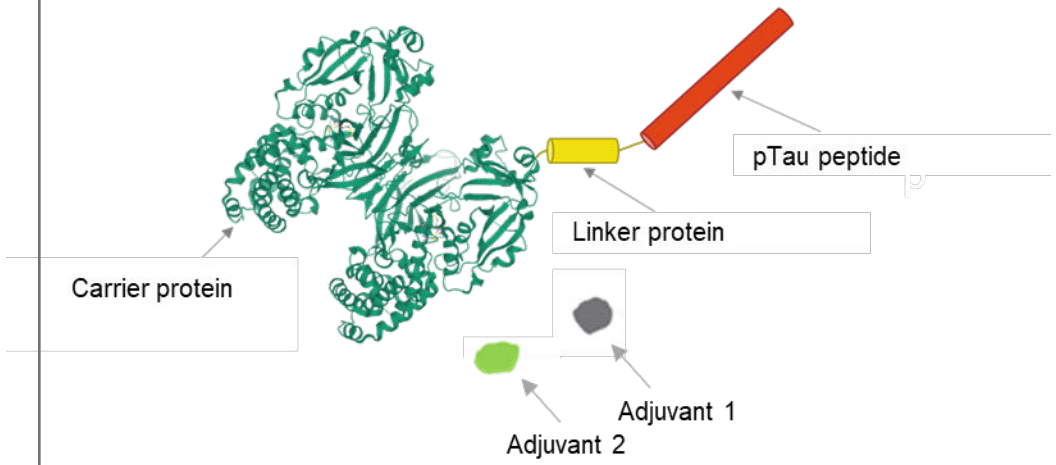
Next generation anti-phospho Tau (pTau) vaccines

Liposomal ACI-35.030 and conjugate JACI-35.054 vaccines

ACI-35.030: SupraAntigen® liposomal platform



JACI-35.054: Carrier protein-Tau peptide

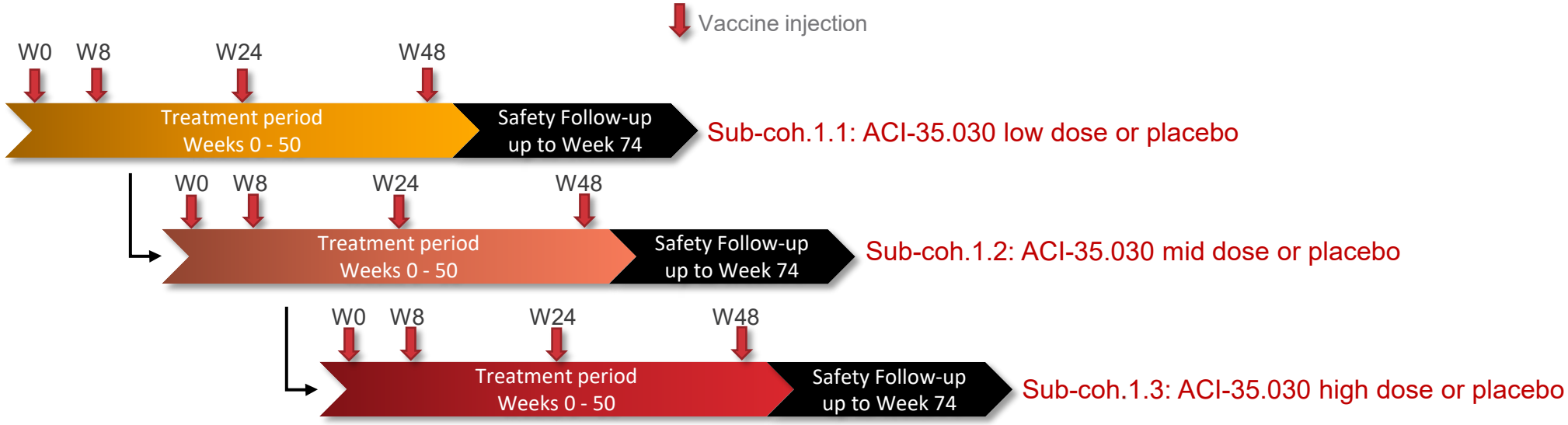


Anti-phospho-Tau vaccine

- The same pTau peptide used in two vaccine formulations

Phase 1b/2a study ACI-35-1802

Study design for Cohort 1 (ACI-35.030 or placebo)

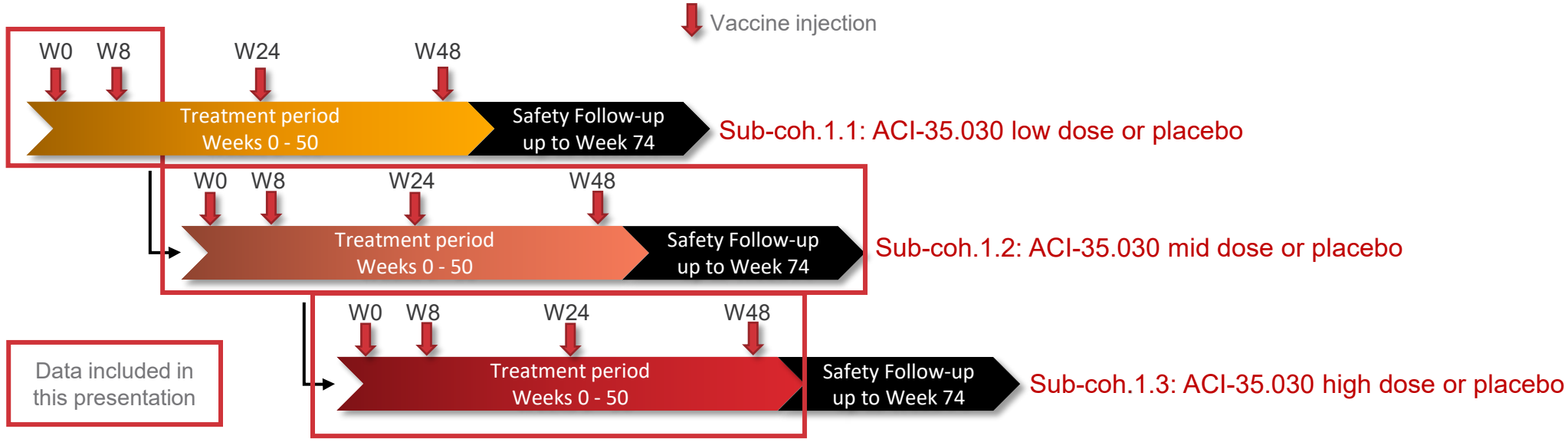


- Design features
  - Mild AD or MCI due to AD (NIA-AA criteria)
  - Sequential dose cohorts with escalating doses
  - 8 AD subjects per study sub-cohort (active/placebo ratio: 3:1)
  - Sub-cohort 1.2 expanded (active/placebo ratio: 3:1), data available up to week 10
- Primary Objectives
  - Safety and tolerability
  - Immunogenicity
- Study status
  - Study sub-cohorts 1.1 to 1.3 are fully recruited
  - Sub-cohort 1.2 expansion fully recruited

(1) ClinicalTrials.gov Identifier: NCT04445831

Phase 1b/2a study ACI-35-1802

Study design for Cohort 1 (ACI-35.030 or placebo)



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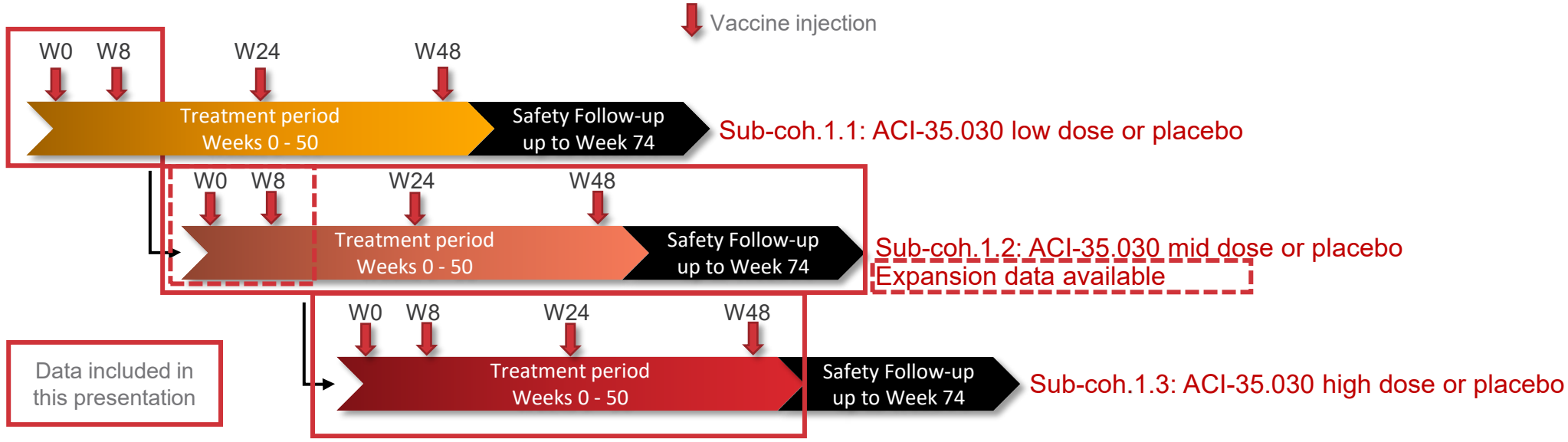

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  - Safety and tolerability
  - Immunogenicity
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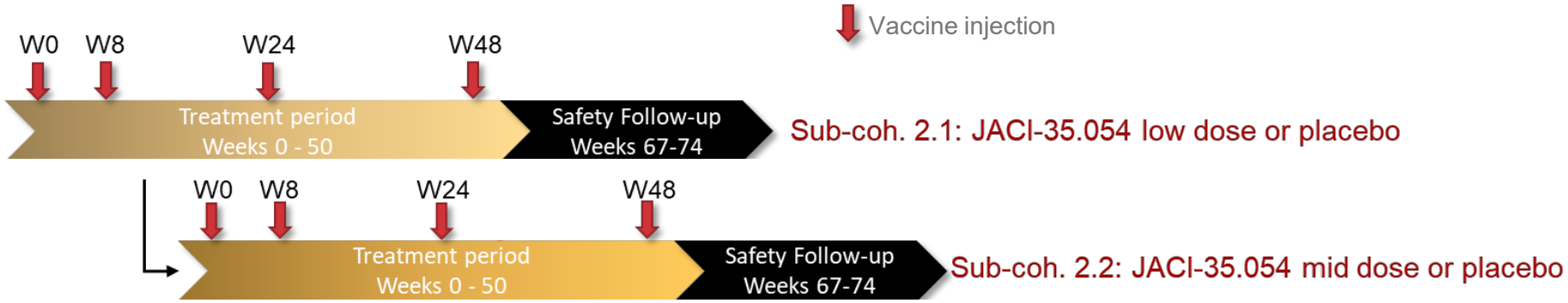
  - Study sub-cohorts 1.1 to 1.3 are fully recruited
  - Sub-cohort 1.2 expansion fully recruited

(1) ClinicalTrials.gov Identifier: NCT04445831

Phase 1b/2a study ACI-35-1802

Study design for Cohort 2 (JACI-35.054 or placebo)

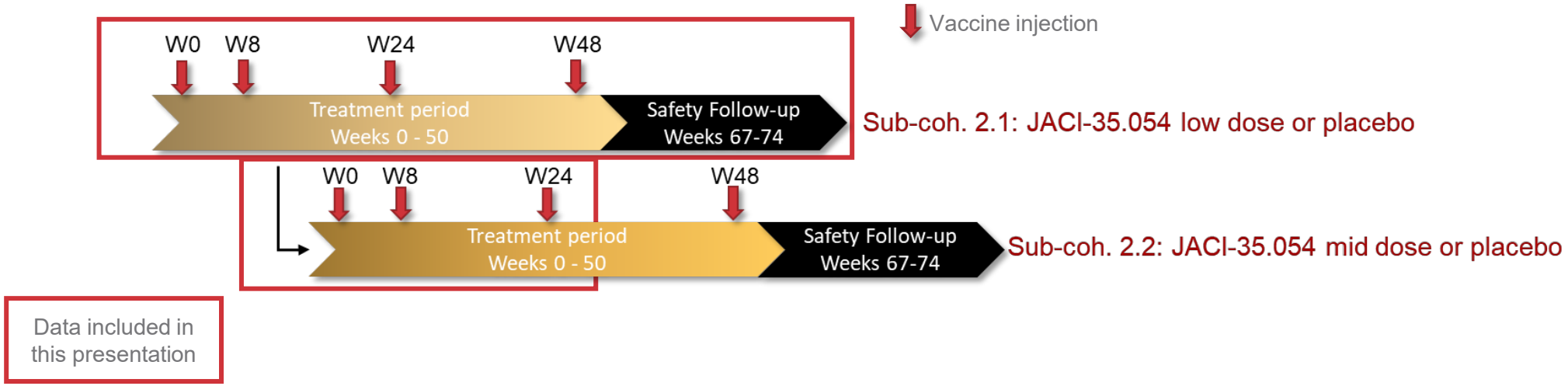


- Design features
  - Mild AD or MCI due to AD (NIA-AA criteria)
  - Sequential dose cohorts with escalating doses
  - 8 AD subjects per study sub-cohort (active/placebo ratio: 3:1)
- Primary Objectives
  - Safety and tolerability
  - Immunogenicity

(1) ClinicalTrials.gov Identifier: NCT04445831

Phase 1b/2a study ACI-35-1802

Study design for Cohort 2 (JACI-35.054 or placebo)



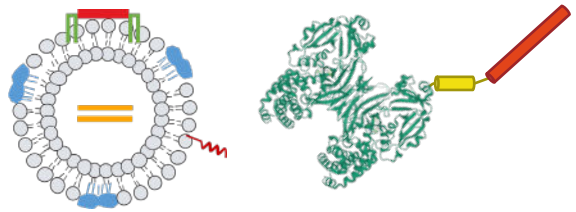
- Design features
  - Mild AD or MCI due to AD (NIA-AA criteria)
  - Sequential dose cohorts with escalating doses
  - 8 AD subjects per study sub-cohort (active/placebo ratio: 3:1)
- Primary Objectives
  - Safety and tolerability
  - Immunogenicity

(1) ClinicalTrials.gov Identifier: NCT04445831

Baseline data

	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)

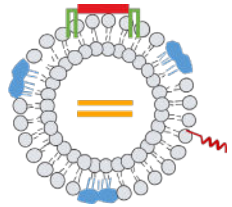
Good safety and tolerability[1]



- Both ACI-35.030 and JACI-35.054 were safe and well tolerated with no study vaccine-related safety concerns observed to date
- No withdrawals due to adverse events or adverse events of severe intensity
- No CNS inflammation or other significant changes reported on MRI
- Two SAEs considered unlikely related to the study vaccine reported in the study to date in the first 2 sub-cohorts
  - episode of acute diverticulitis
  - sick sinus syndrome (requiring pacemaker)
- Two safety unrelated study withdrawals in sub-cohort 1.1
  - resulting study data from cohort 1.1 can only be shown until week 10 (2 weeks after 2nd vaccination) to keep study blind

(1) Data cut-off at end of September 2022

ACI-35.030 shows a fast, high and sustained response rate



Vaccine injection

Sub-cohort 1.1 (low dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	**83.3%**	33.3%	33.3%	NA	NA	NA	NA	NA
Anti-pTau IgG	**100%**	**100%**	**100%**	NA	NA	NA	NA	NA
Anti-ePHF IgG	66.7%	**83.3%**	**83.3%**	NA	NA	NA	NA	NA
Sub-cohort 1.2 (mid dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	**89.5%**	63.2%	78.9%	16.7%	50%	16.7%	16.7%	16.7%
Anti-pTau IgG	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Anti-ePHF IgG	73.7%	73.7%	**94.7%**	66.7%	**100%**	**83.3%**	**100%**	50%
Sub-cohort 1.3 (high dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	**83.3%**	50%	66.7%	16.7%	50%	NA	NA	NA
Anti-pTau IgG	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**NA**
Anti-ePHF IgG	66.7%	33.3%	**83.3%**	50%	66.7%	**NA**	**NA**	**NA**

Responder rates
- ■ 100-80%
- ■ <80-50%
- ■ <50%

Prespecified responder definitions: Responders were defined as higher than a pretreatment value multiplied by a threshold factor (>~2x)

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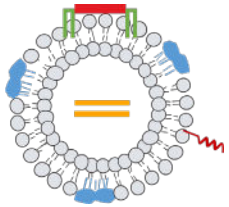
ACI-35.030 shows a fast, high and sustained response rate



Vaccine injection

Sub-cohort 1.1 (low dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	**83.3%**	33.3%	33.3%	NA	NA	NA	NA	NA
Anti-pTau IgG	**100%**	100%	100%	NA	NA	NA	NA	NA
Anti-ePHF IgG	**66.7%**	83.3%	83.3%	NA	NA	NA	NA	NA
Sub-cohort 1.2 (mid dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	**89.5%**	**63.2%**	**78.9%**	**16.7%**	**50%**	**16.7%**	**16.7%**	**16.7%**
Anti-pTau IgG	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Anti-ePHF IgG	**73.7%**	**73.7%**	**94.7%**	**66.7%**	**100%**	**83.3%**	**100%**	**50%**
Sub-cohort 1.3 (high dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	**83.3%**	50%	66.7%	16.7%	50%	NA	NA	NA
Anti-pTau IgG	**100%**	100%	100%	100%	100%	100%	100%	NA
Anti-ePHF IgG	**66.7%**	33.3%	83.3%	50%	66.7%	NA	NA	NA

Responder rates
- 100-80%
- <80-50%
- <50%

- High responder rates after first and all following vaccinations across all dose levels
- 100% response rate for pathological (ePHF) and phosphorylated Tau at the mid-dose after 1 year treatment period
- Higher responder rate on ePHF for mid-dose compared to high dose

Prespecified responder definitions: Responders were defined as higher than a pretreatment value multiplied by a threshold factor (>~2x)

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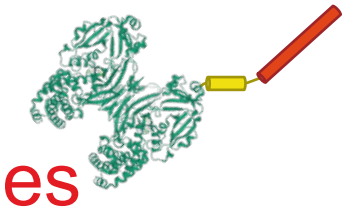
JACI-35.054 shows a delayed Ab[1] response which increases over time, towards both phospho- and non-phospho Tau species



Vaccine injection

Sub-cohort 2.1 (low dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	66.7 %	83.3 %	100 %	100 %	100 %	100 %	100 %	100 %
Anti-pTau IgG	50 %	66.7%	100 %	100 %	100 %	100 %	100 %	100 %
Anti-ePHF IgG	0 %	0 %	66.7 %	50 %	83.3 %	66.7%	83.3%	66.7 %
Sub-cohort 2.2 (mid dose)								
	Week 2	Week 8	Week 10	Week 24	Week 26	Week 48	Week 50	Week 74
Anti-Tau IgG	66.7 %	66.7 %	100 %	100 %	100 %	NA	NA	NA
Anti-pTau IgG	66.7%	83.3%	100 %	100 %	100 %	NA	NA	NA
Anti-ePHF IgG	16.7 %	16.7 %	83.3 %	50 %	100 %	NA	NA	NA

Responder rates
- 100-80%
- <80-50%
- <50%

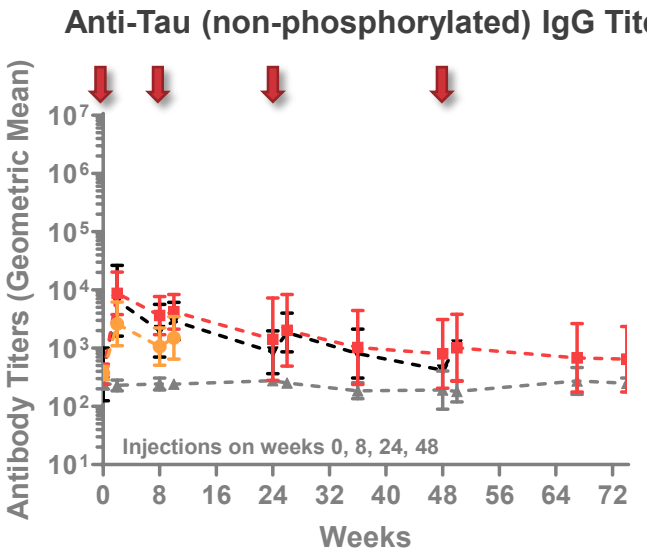
- 2 immunizations required to achieve high response rate on ePHF
- 83.3-100 % response rate for all Tau species after 1 year treatment period
- Lower ePHF responder rate
- Limited dose effect observed

Prespecified responder definitions: Responders were defined as higher than a pretreatment value multiplied by a threshold factor (>~2x)

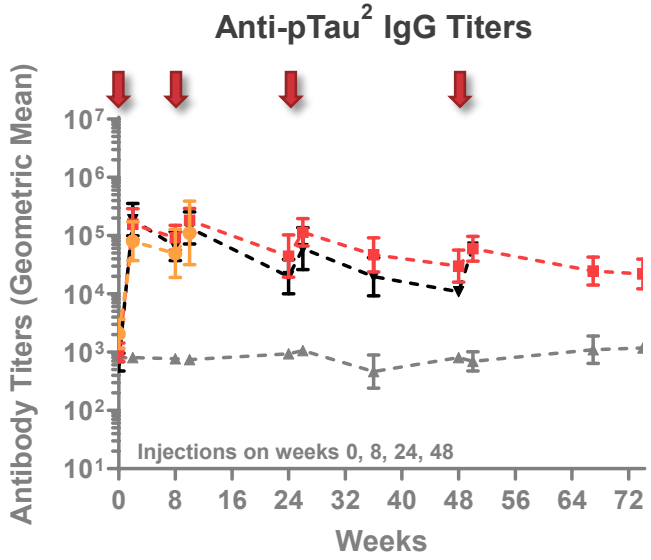
ACI-35.030: potent Ab[1] response with preference for pathological Tau

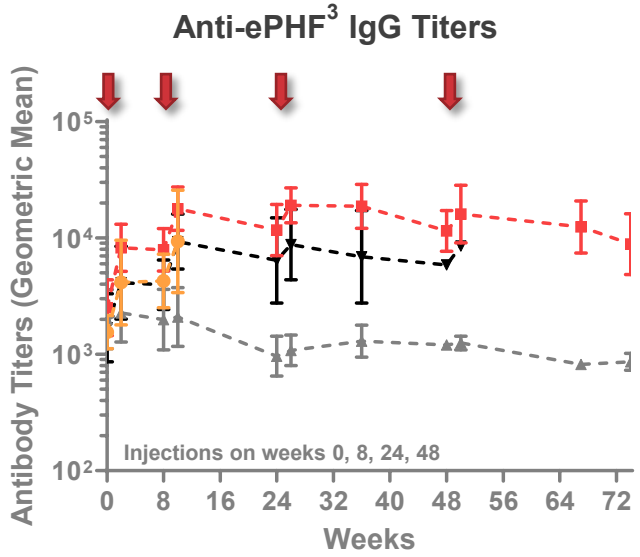
Fast, high, phospho-Tau-specific, and boostable antibody response

Non-Phosphorylated Tau



Phosphorylated & Pathological Tau species



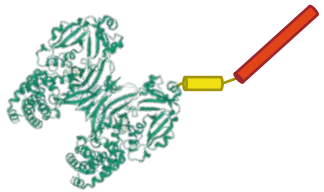


low dose
high dose
mid dose
Placebo
Vaccine injection

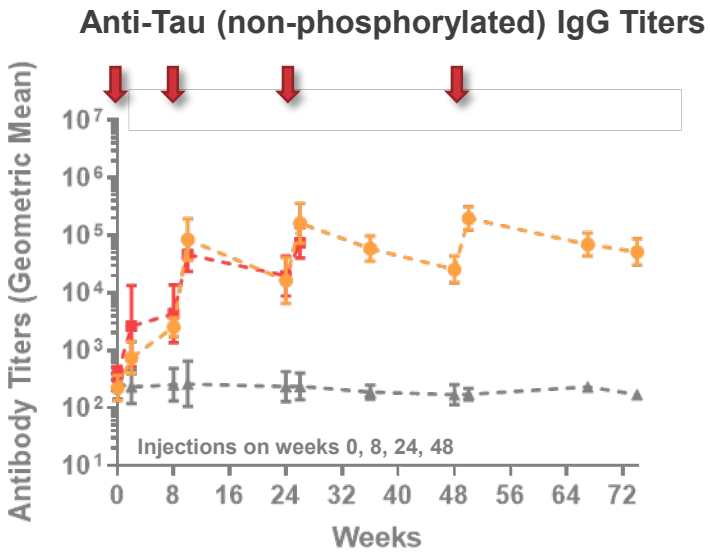
- Strong antibody response to all measured species
- Strong preference develops for pathological Tau
- High and boostable anti-ePHF IgG; maintained high anti-pTau IgG; over time lower anti-Tau IgG

(1) Antibody; (2) phosphorylated Tau; (3) Enriched paired helical filaments

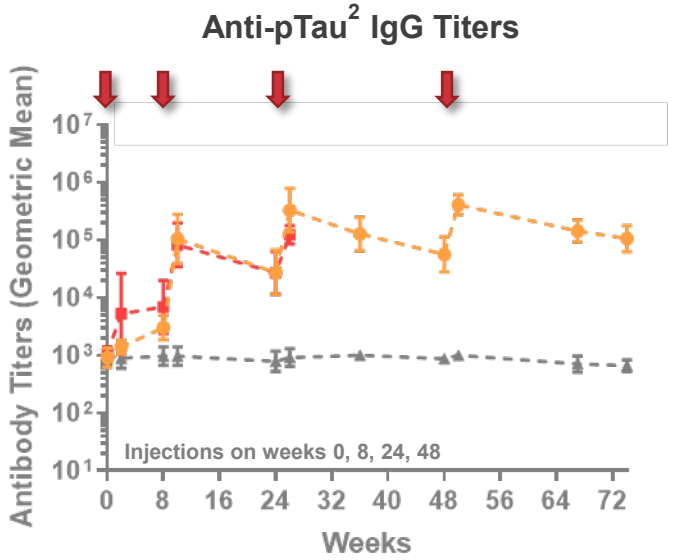
JACI-35.054: potent Ab[1] response without phospho-specificity for Tau

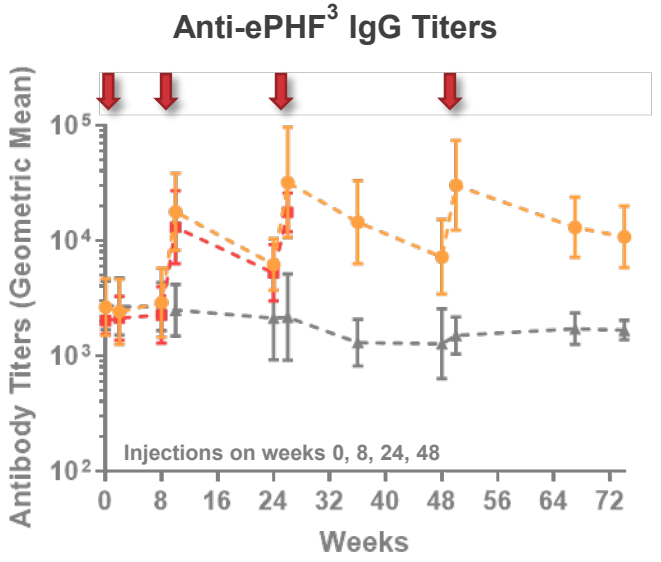


Non-Phosphorylated Tau



Phosphorylated & Pathological Tau species





low dose
mid dose
Placebo
Vaccine injection

- Good antibody response to all measured species
- No preference development for pathological Tau, with maintained high titers against normal Tau
- Detectable anti-ePHF antibody levels require 2 immunizations; variable responses in patients

(1) Antibody; (2) phosphorylated Tau; (3) Enriched paired helical filaments

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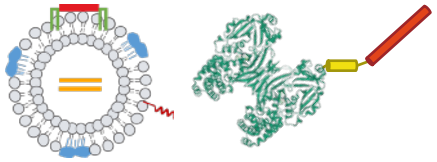
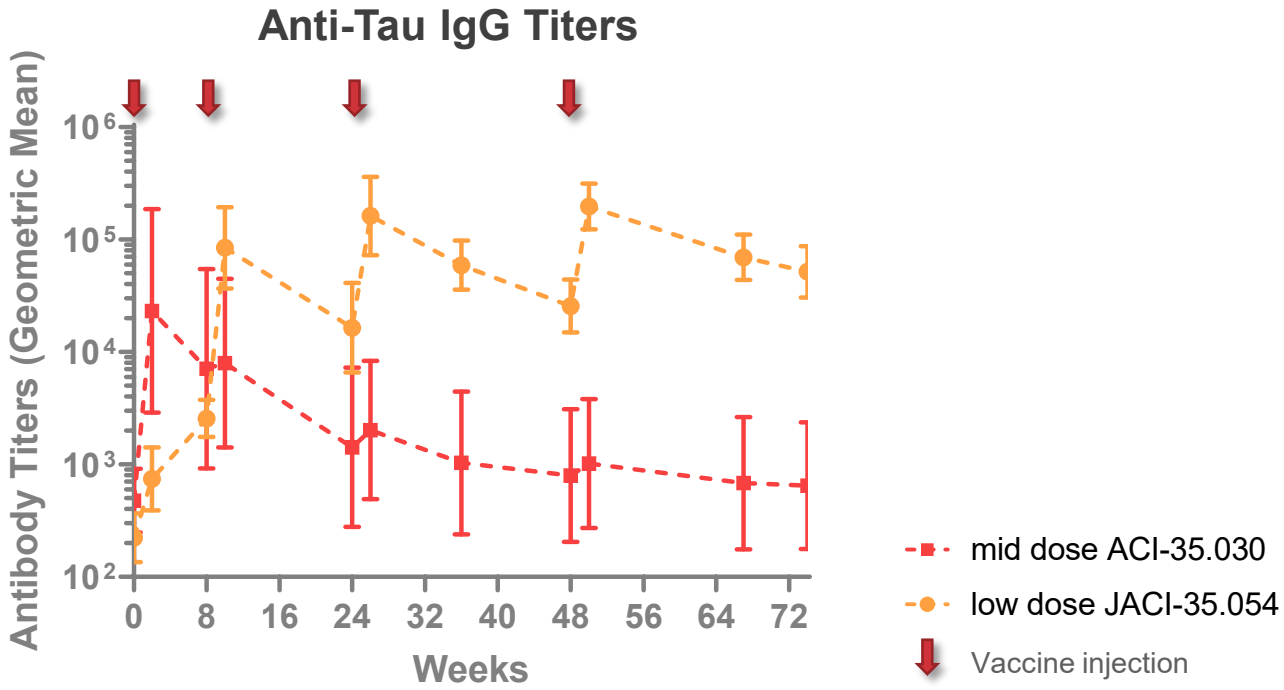
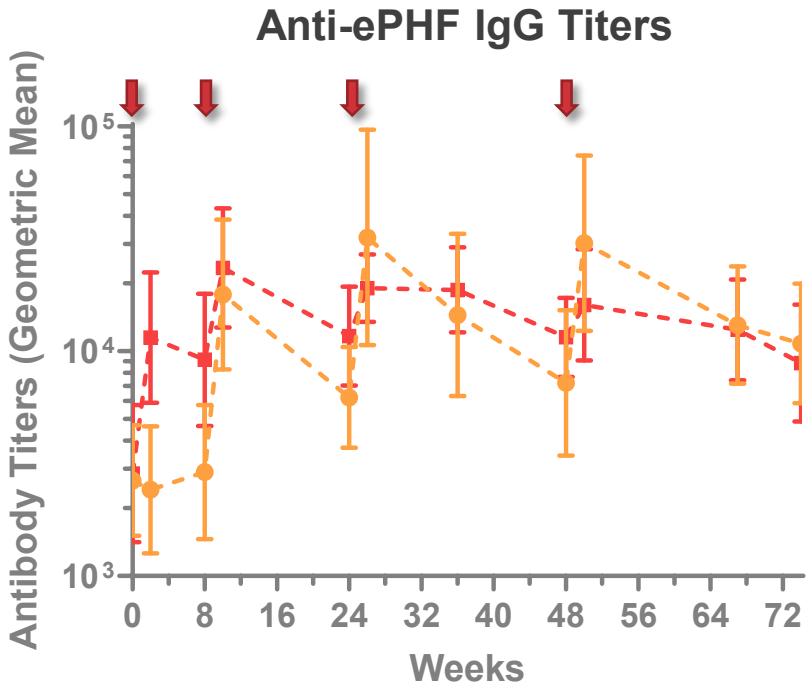
Desired antibody response: ACI-35.030[1] compared to JACI-35.054

Superior specificity for pathological Tau







1 ACI-35.030 antibody response preferentially targets pathological Tau species over normal Tau

2 ACI-35.030 antibody response in 100% of patients after 1st injection compared to 50% with JACI-35.054

3 ACI-35.030 induced anti-ePHF antibodies - longer apparent half-lives, less variability, lower peak-to-trough ratios

4 ACI-35.030 shows excellent overall performance in elderly patients with outstanding safety and tolerability

(1) ACI-35.030 original sub-cohort 1.2 data

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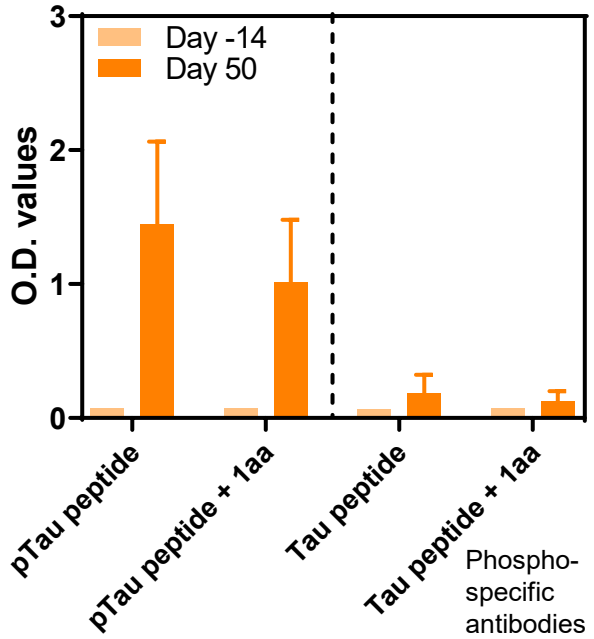
OC39 - Advantages of next generation SupraAntigen® platform liposomal vaccines to immunize against pathological targets of Alzheimer's disease

Marija Vukicevic [1], Emma Fiorini [1], David Hickman [1], Rakel Carpintero [2], Marcela Rincon [2], Maria Pilar Lopez-Deber [2], Maxime Ayer [2], Stefanie Siegert [2], Chiara Babolin [2], Eva Gollwitzer [2], Saskia Delpretti-Anex [2], Piergiorgio Donati [2], Johannes Streffer [2,3], Andrea Pfeifer [2], Marie Kosco-Vilbois [2]
[1]Ac Immune SA - Lausanne (Switzerland), [2]AC Immune SA - Lausanne (Switzerland), [3]University of Antwerp - Antwerpen (Belgium)

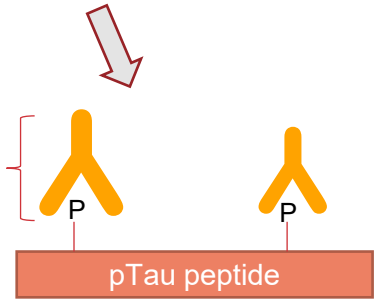
Friday, DECEMBER 2

Characterizing further epitope coverage

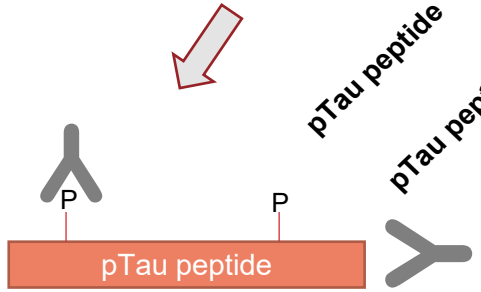
Truncation specific antibodies differentiate ACI-35.030 and JACI-35.054 in NHPs

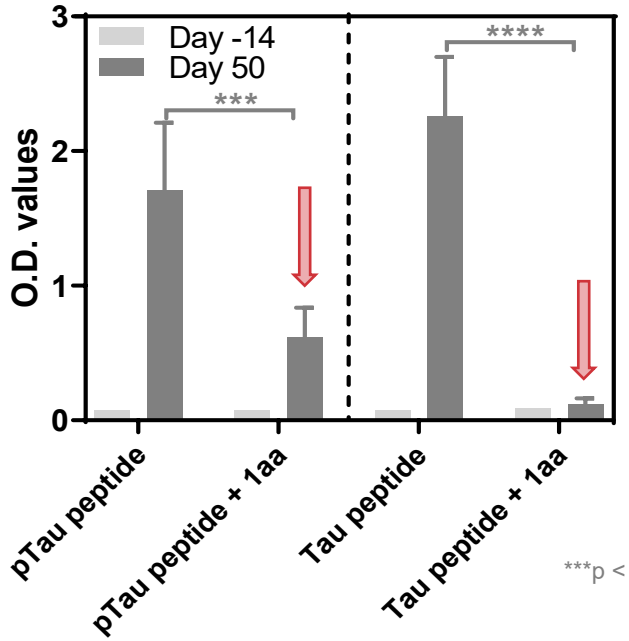


ACI-35.030



JACI-35.054





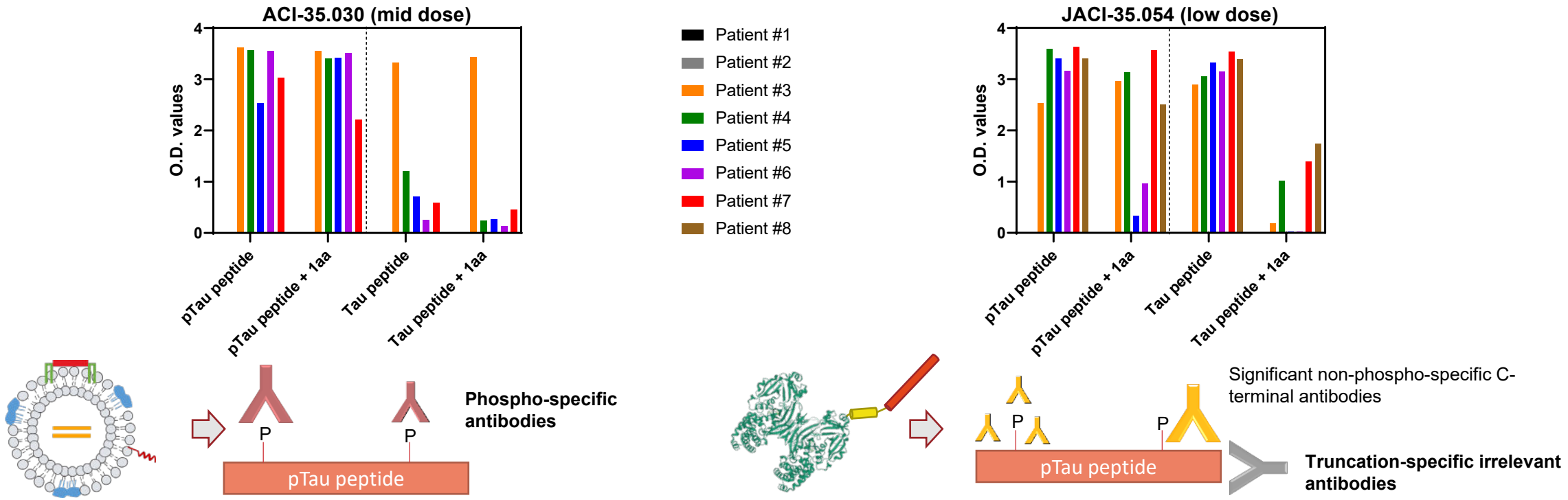
***p < 0.001, ****p < 0.0001

Truncation-specific nonfunctional antibodies

NHP: non-human primates; aa: amino acid
Analysis: Day 50 (3 weeks after the 2nd immunization)

- Addition of one amino acid to the antigenic peptide does not change the binding of ACI-35.030 induced Abs
- Addition of one amino acid to the antigenic peptide decreases the binding of JACI-35.054 induced Abs, suggesting the abundance of truncation-specific irrelevant antibodies

Presentation of B-cell peptide on liposomal ACI-35.030 drives Ab[1] response towards pathological Tau species



- ACI-35.030 vaccine induces wide range of Abs covering the pTau antigenic sequence
- JACI-35.054 induces antibodies mostly binding to the very C-terminus of the peptide in a non-phospho specific manner

(1) aa, amino acid; (2) antibody

Summary

01	ACI-35.030 selected for further development	▪ ACI-35.030 the superior vaccine candidate compared to JACI-35.054 in terms of: ▪ effectively targeting pathologic forms of Tau ▪ faster antibody responses
02	Sustainable long-term antibody response supports prevention	▪ Boostable and durable antibody response over the 50-week treatment period supporting a disease prevention approach
03	Safe and well-tolerated	▪ Excellent safety and tolerability profile, inducing IgG responses to the immunizing peptide as well as AD brain-derived pathological Tau
04	Excellent performance of SupraAntigen® platform	▪ SupraAntigen® generates potent and highly target-specific antibodies in the context of outstanding safety and tolerability

Julien Mermoud
Olivier Sol
Marija Vukicevic
Emma Fiorini
Eva Gollwitzer
Valérie Hliva
David Hickman
Julian Gray
Piergiorgio Donati
Maria Pilar Lopez Deber
Julien Rongère
Andrea Pfeifer
Marie Kosco-Vilbois
Philip Scheltens

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AC Immune

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Shifting the treatment paradigm for neurodegenerative diseases towards Precision Medicine and disease prevention