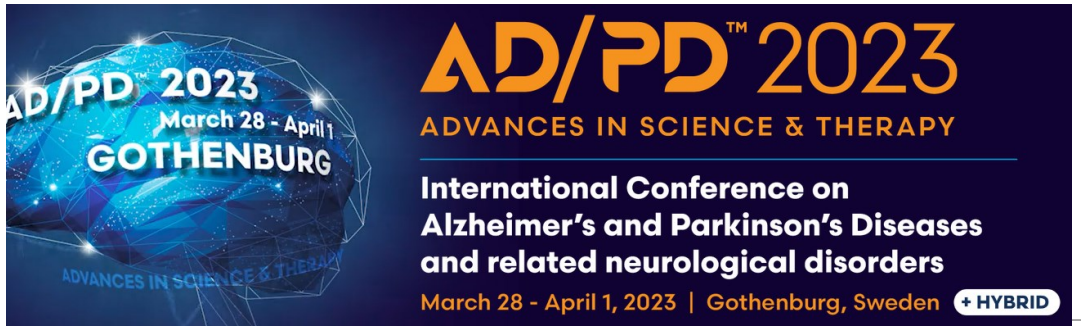
ABATE study – utilizing biomarker-based development for optimized ACI-24, a novel candidate vaccine for the treatment and prevention of Alzheimer's disease

Olivier Sol[1]; Bénédicte Lê[1]; Agnes Feige[1], Jonathan Wagg[1]; Nicolas Fournier[1]; Elena Valatsou[1]; Saskia Delpretti[1]; Julien Rongère[1]; Emma Fiorini[1]; Marija Vukicevic[1]; Julian JG. Gray[1]; Valérie Hliva[1]; Marie Kosco-Vilbois[1], Andrea Pfeifer[1], Johannes Streffer[1,2]

1) AC Immune SA, Lausanne, Switzerland
2) University of Antwerp, Belgium



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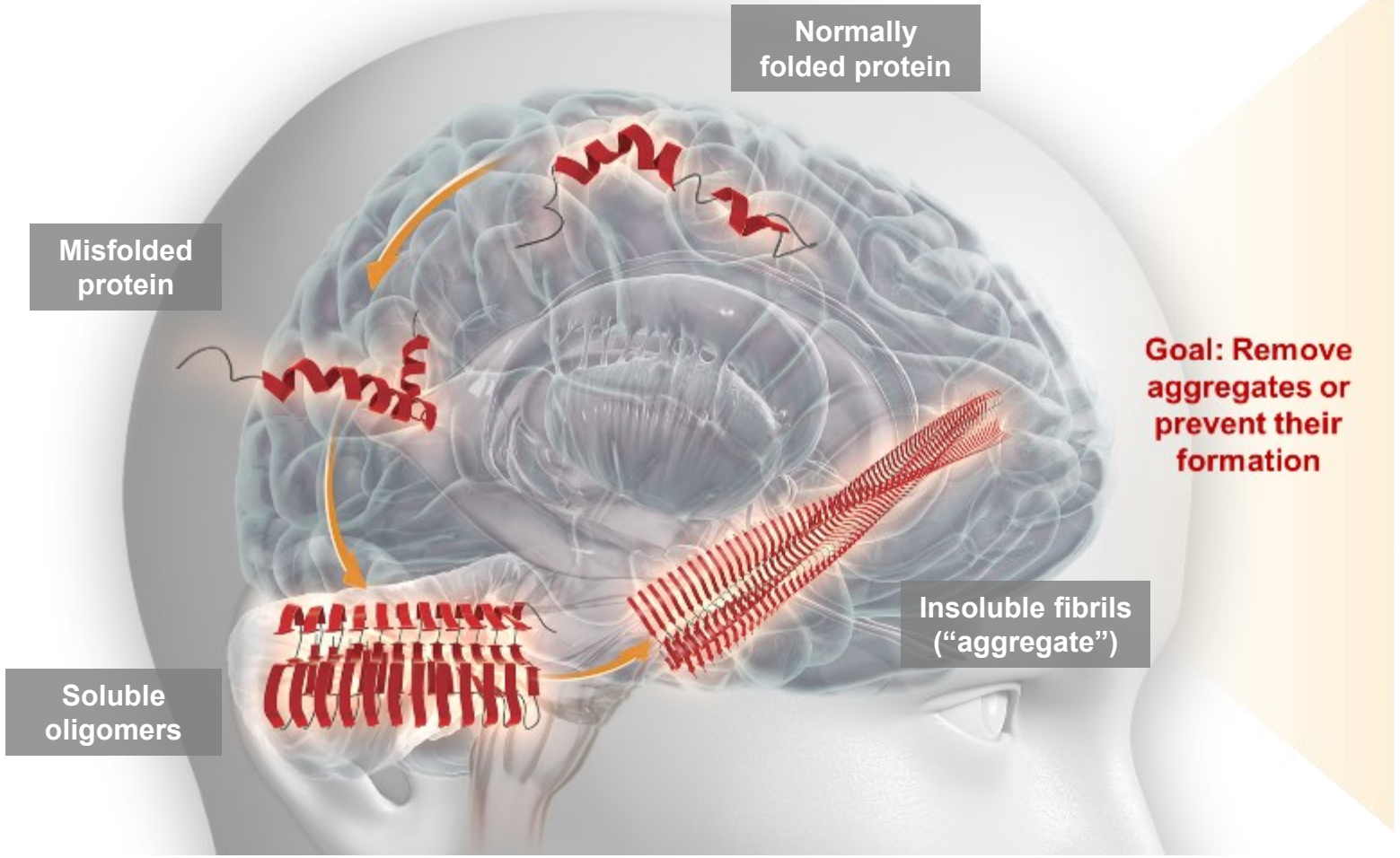
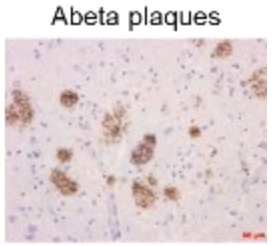
Conflict of interest disclosure

Johannes Streffer is an employee and shareholder of AC Immune and participates in the stock incentive plan.

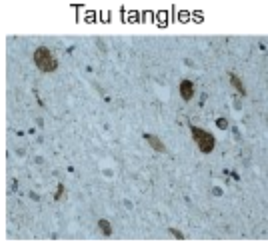
Misfolded proteins: Leading causes of neurodegenerative diseases

Abeta, Tau, a-synuclein, and TDP-43[1] are important NDD[2] drug targets

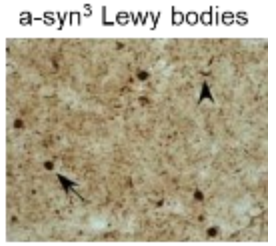




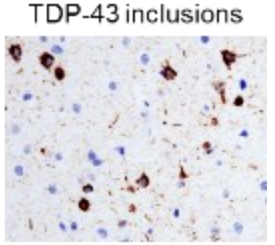
Alzheimer's disease



Alzheimer's disease, FTD[4]-Tau



Parkinson's disease

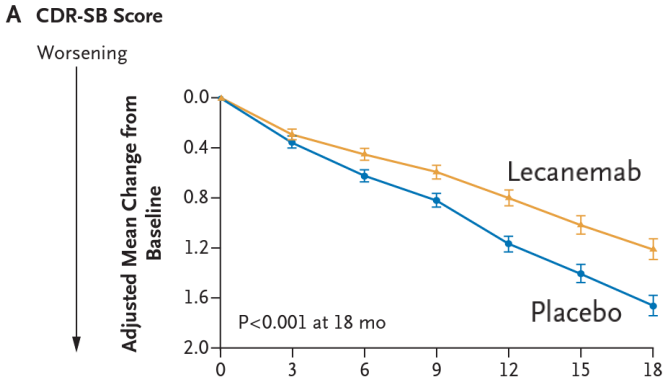


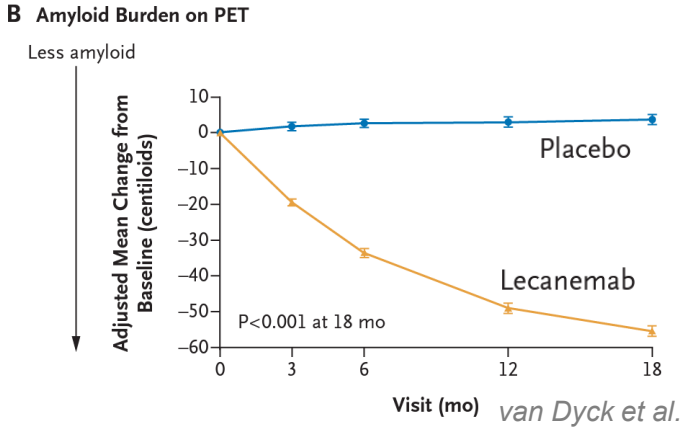
LATE[5] dementia, ALS[6], FTD[4]-TDP

Refs: Soto 2003, http://www.alz.org/brain; Nag *et al.* Acta Neuropathologica Communications (2018) 6:33;
(1) TAR DNA-binding protein 43; (2) Neurodegenerative disease; (3) a-synuclein; (4) Fronto Temporal Dementia (5) Limbic-predominant age-related TDP-43 encephalopathy; (6) Amyotrophic lateral sclerosis

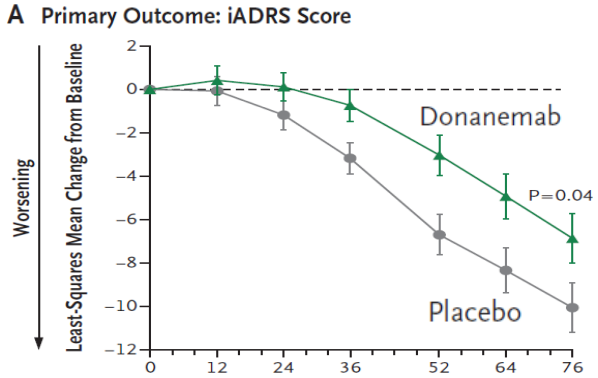
Successful Immune therapy for early intervention in Alzheimer's Disease

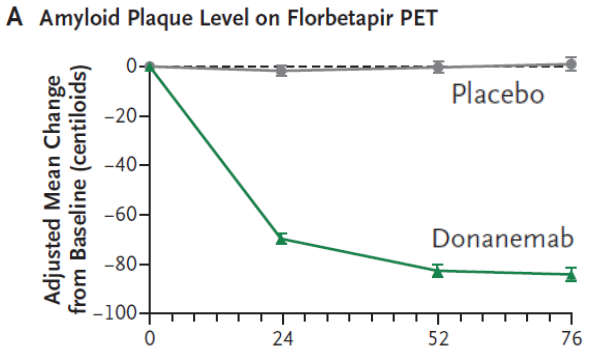
Demonstration that lowering of Amyloid PET burden is valid as a biomarker for clinical effect



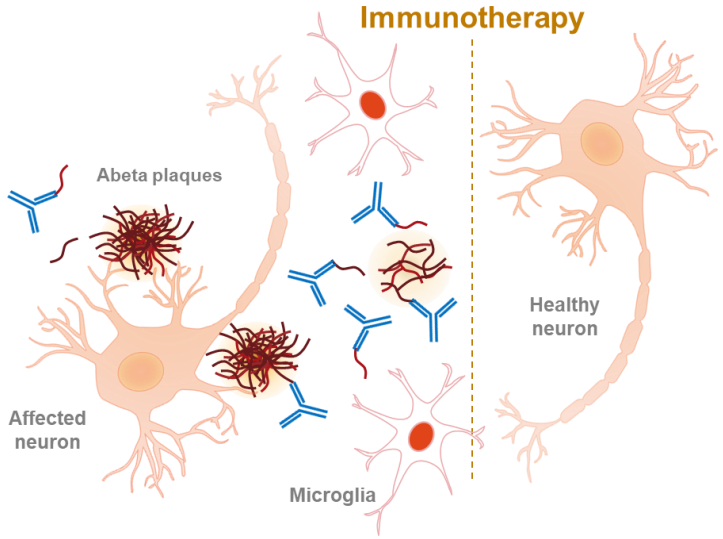


van Dyck et al., NEJM 2022





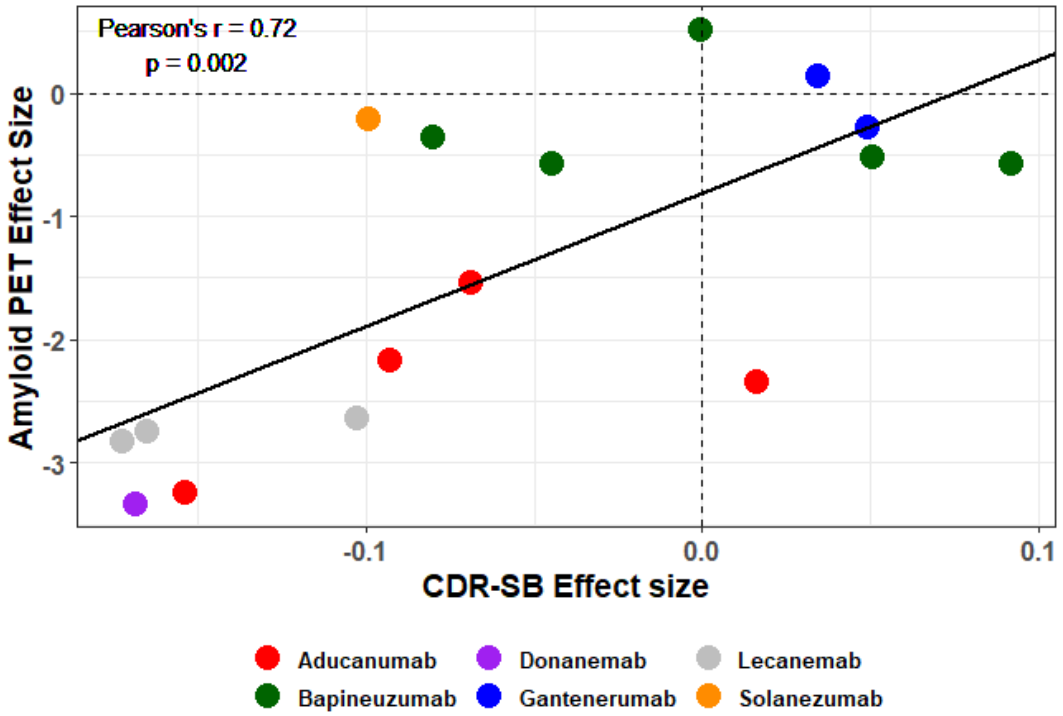
Mintun et al., NEJM 2021

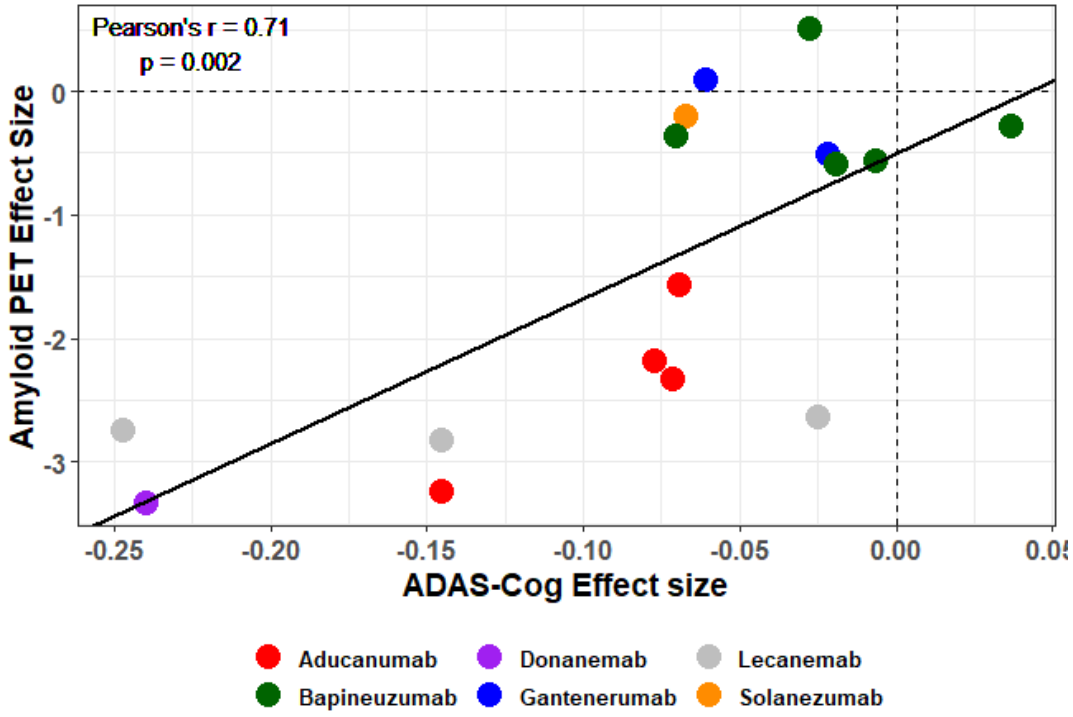


- Targeting small aggregates such as Abeta oligomers or fragments such as Abeta 1-42 and pyroglutamate Abeta3-42 (pGlu-Abeta3-42) has demonstrated clinical utility
- Building on recent clinical proof-of-concept for Abeta mAbs

Amyloid PET as a surrogate biomarker for clinical effect

Correlations between amyloid PET and ADAS-Cog and CDR-SOB effect sizes (across studies)





Note that data for amyloid PET SUVR were reported only for sub-populations of the original Studies. Each correlation relies on the assumption that effect sizes for PET in these sub-populations are representative of those for the entire populations.

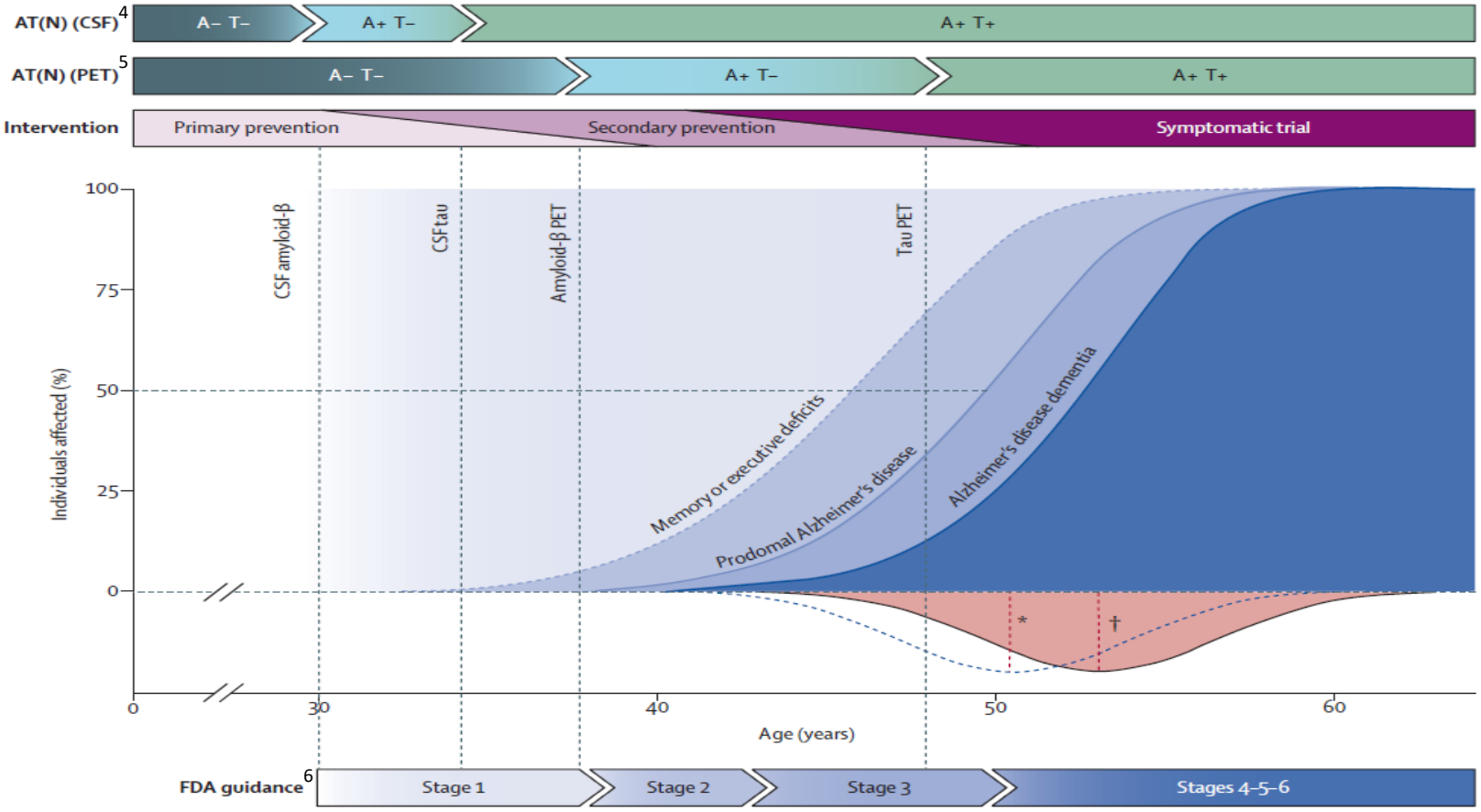
- NIH meta-analysis[1] updated with data from Trailblazer (Phase 2: Donanemab), Clarity (Phase 3: Lecanemab) and Study 201 (Phase 2: Lecanemab) trials
- Clinical improvements apparent - amyloid PET reductions correlate with small effect sizes

1: Avgerinos et al, Aging Research Reviews, 68 (2021). National Institute on Aging, NIH Study. Meta-analysis based on reported outcomes for 12 Phase III parallel double-blind Placebo-controlled Trials of mAbs targeting Abeta.

Lifelong accumulation of AD[1] neuropathology in people with DS[2]

AD biomarker patterns in people with DS closely resemble patterns of sporadic AD and ADAD[3]

- AD associated with DS is a genetic form of dementia
  - 75-100% of people with DS have AD like symptoms by age 60.
  - neuropathologic hallmarks of AD also present in AD associated with DS
  - similar pathophysiology and biomarkers as compared to autosomal dominant AD
- Predictive, age-associated biomarker pattern supports prevention studies

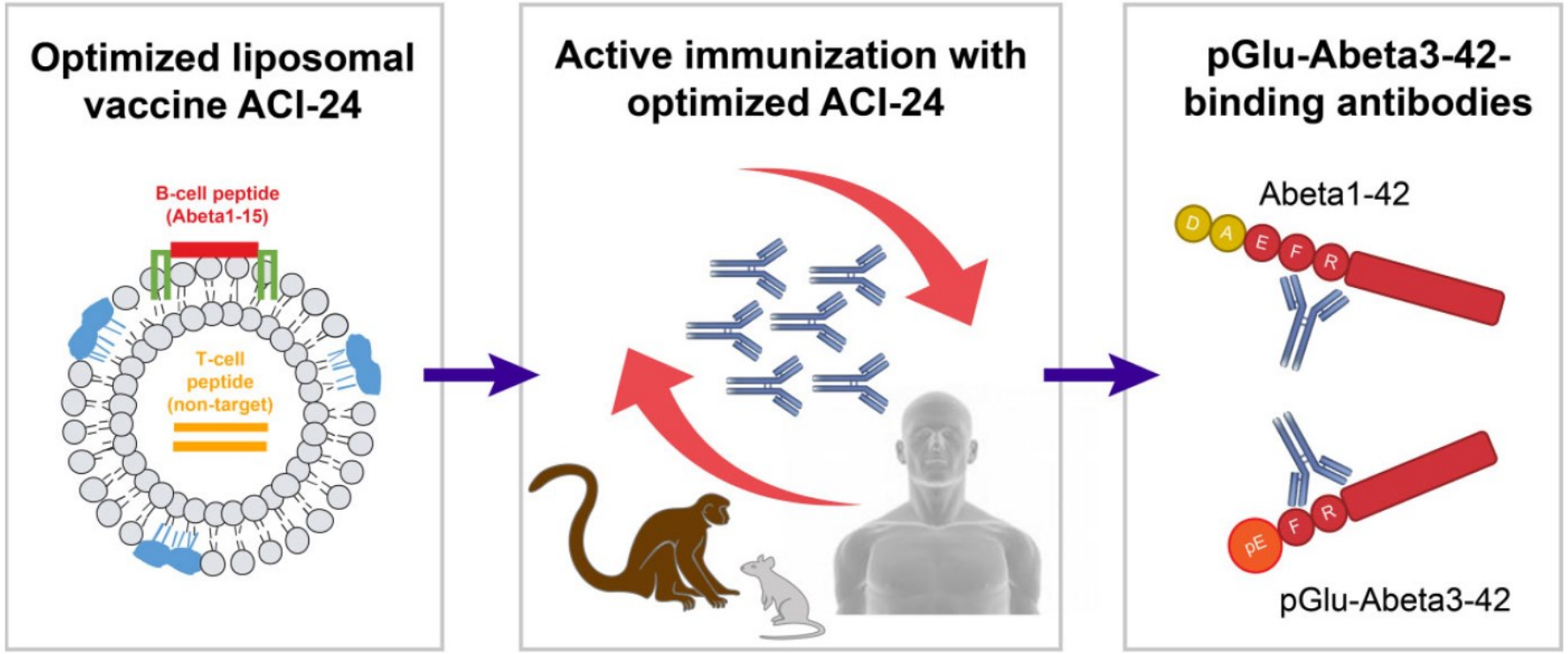


Fortea et al., 2021

(1) Alzheimer's disease; (2) Down syndrome; (3) autosomal dominant AD; (4) A; Amyloid biomarker; T; Tau biomarker; N; Neurodegeneration biomarker; CSF; Cerebro Spinal Fluid; (5) PET; Positron Emission Tomography (6) FDA; Food and Drug Administration

ACI-24 – Active immunization for early intervention in Alzheimer's Disease

An amyloid beta vaccine that safely drives immunity to key pathological species in Alzheimer's disease: pyroglutamate and amyloid beta



M. Vukicevic et al., Brain Communications, 2022

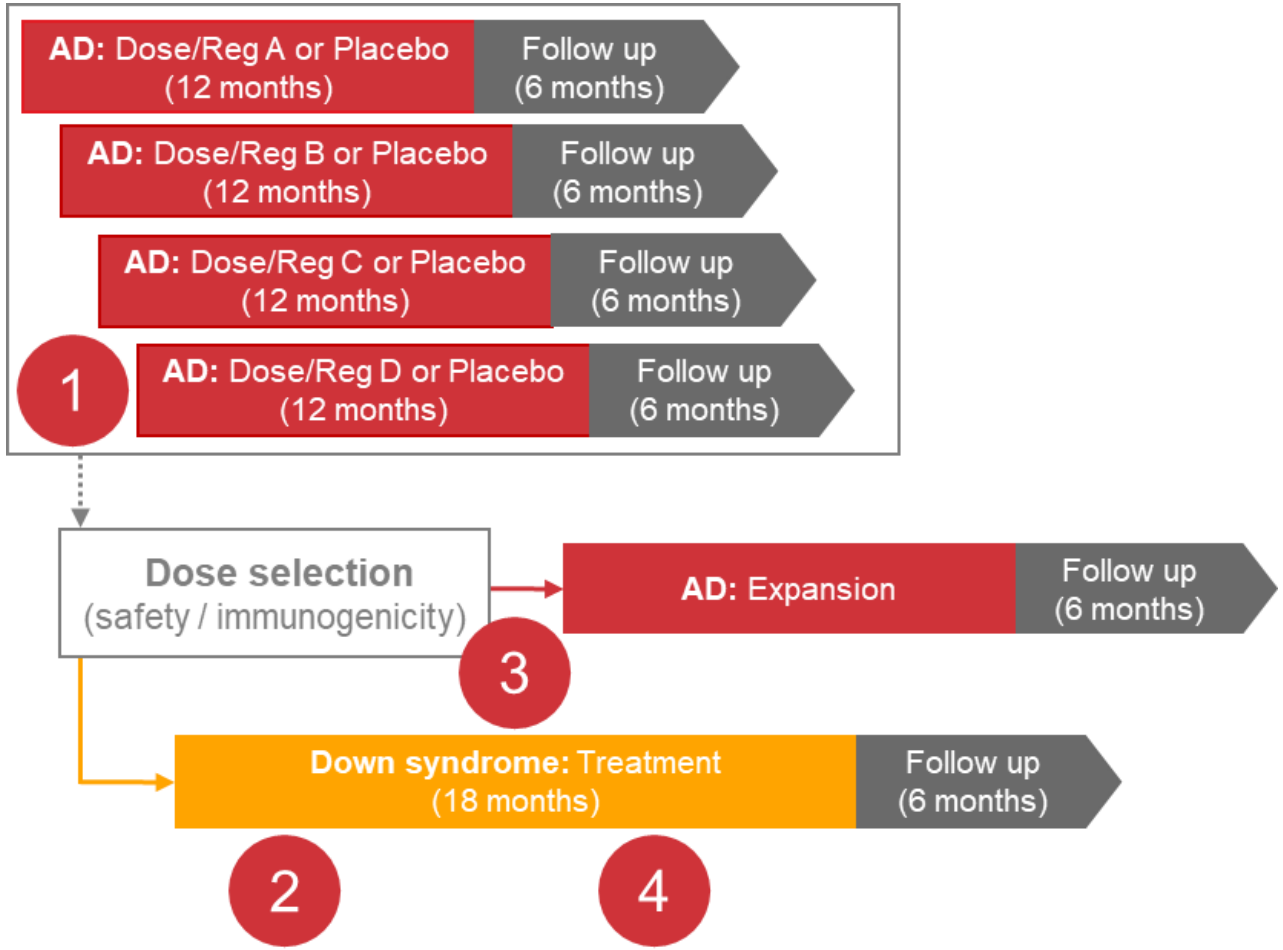
- Initial clinical data have demonstrated safety and encouraging pharmacodynamic response, both in sporadic AD and adults with DS, a specifically vulnerable population predisposed to developing AD.
- ACI-24 has strong immunogenicity against key toxic species including oligomers, Abeta 1-42 and pGlu-Abeta3-42

ABATE study – clinical trial design in sporadic AD and in people with DS

Biomarker based design allows de-risking and acceleration

Trial Design features

- Innovative, translational clinical trial design evaluating ACI-24.060 in sporadic AD and in people with DS to understand:
  - immunogenic properties
  - pharmacodynamic effects
- Staggered inclusion of prodromal sporadic AD and people with DS
- Amyloid PET positivity used as a biomarker for study inclusion in both populations
- Possibility to expand one initial cohort with prodromal AD
- Early assessment of safety and immunogenicity
- Trial design supports parallel development in sporadic AD and in people with DS

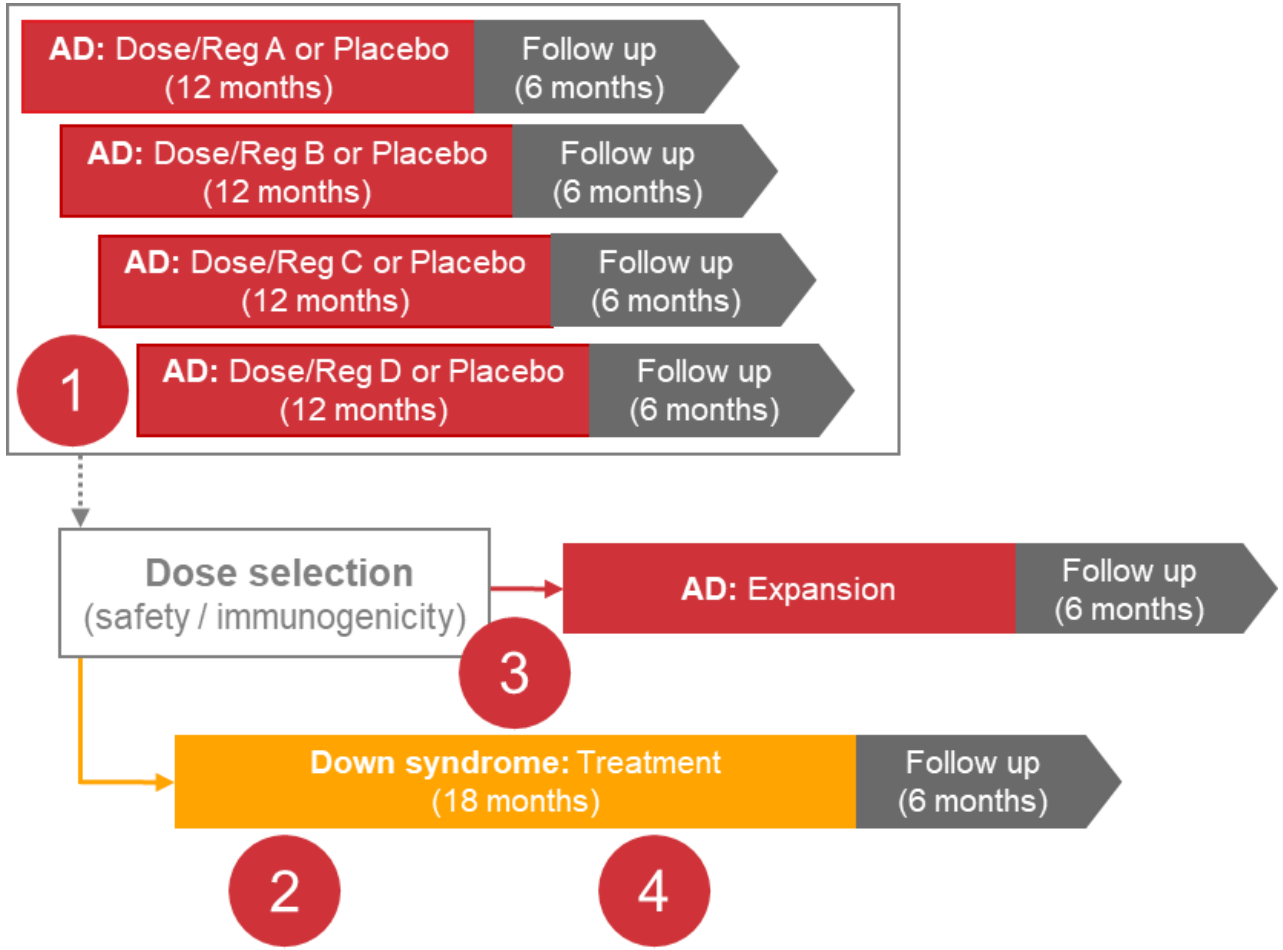


ABATE study – clinical trial design in sporadic AD and in people with DS

Biomarker based design allows de-risking and acceleration

Interim analyses and decision points

- Biomarker-based design includes multiple interim analyses, enabling early, informed decision making
- Delivering four distinct decision points:
  1. Safety and Antibody titers in AD
  2. Safety and Antibody titers in DS
  3. Amyloid PET lowering in AD
  4. Amyloid PET lowering in DS
- Multiple opportunities for acceleration:
  - expansion of the study
  - initiation of pivotal trials, and/or
  - initiation of prevention trials

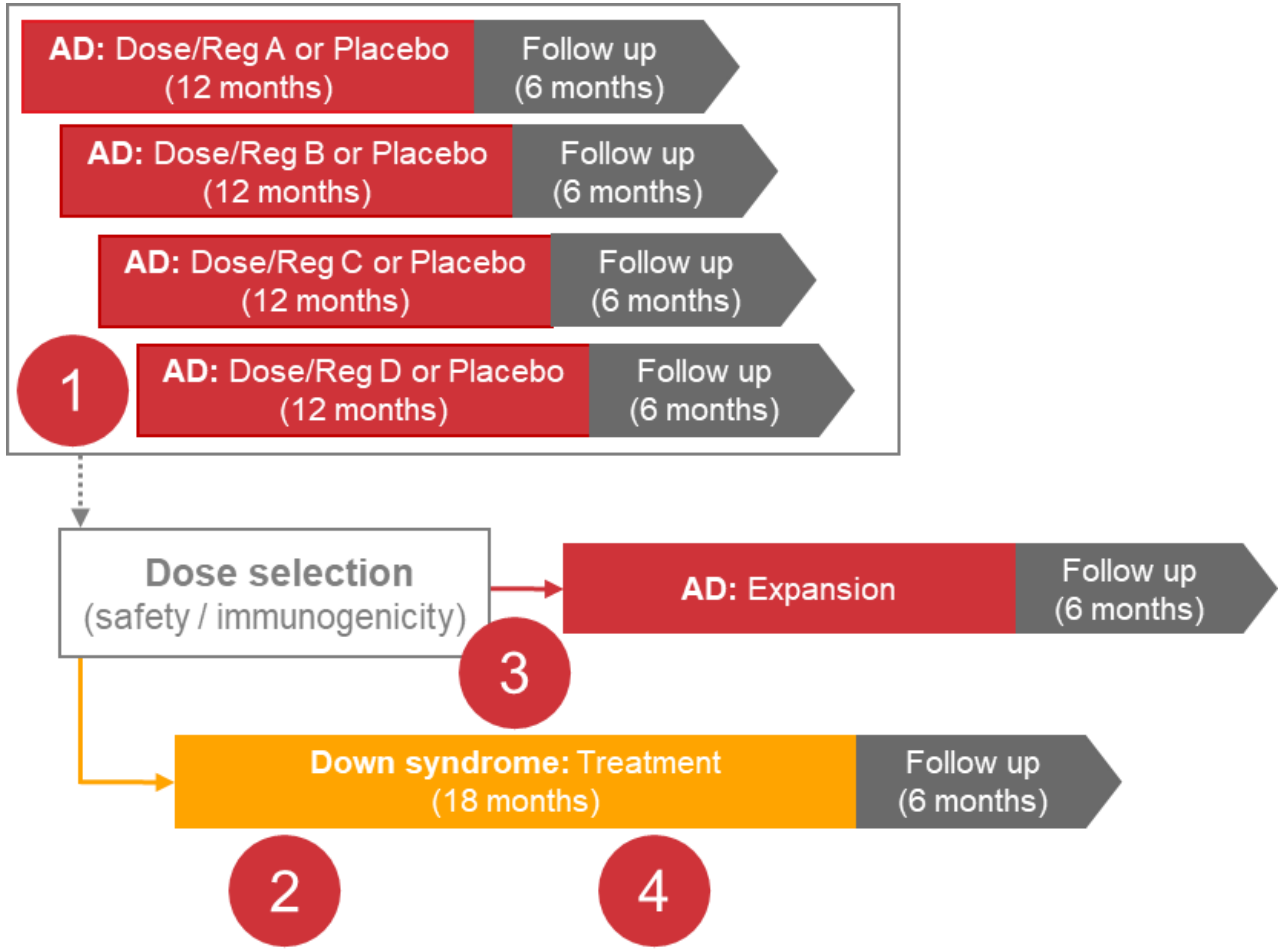


ABATE study – clinical trial design in sporadic AD and in people with DS

Biomarker based design allows de-risking and acceleration

Study status and progress

- ACI-24.060 elicited an anti-Abeta antibody response in ABATE's first, low-dose cohort
- ACI-24.060 was generally well tolerated with no safety concerns observed
- Started dosing in a second, higher dose Alzheimer's cohort is ongoing
- Screening of cohort of study participants with DS cleared to begin
- Further safety and immunogenicity findings from ABATE cohorts expected in H2 2023
- Initial data on amyloid plaque reduction measured via PET imaging anticipated in 2024



ABATE study – biomarker-based development for ACI-24.060

Novel candidate vaccine for the treatment and prevention of Alzheimer's disease

Biomarker-based design	▪ Biomarker-based translational medicine benefits from improved clinical evaluation of targeting of toxic Abeta fragments and aggregates in mAb trials
Precision Medicine	▪ Clearly defined populations with predictable biomarkers and progression patterns, like prodromal AD and AD in DS, allow Precision Medicine approach
Treatment and Prevention	▪ Abeta is now validated as a target ▪ Amyloid PET burden is established as surrogate biomarker to evaluate treatment effect and inform prevention studies
ACI-24.060 vaccine	▪ ACI-24.060 has added non-target T-helper peptides ▪ Vaccines may provide significant benefits with fewer administrations, better compliance and lower costs
Acceleration and de-risking	▪ Innovative trial design for ACI-24.060 enables an efficient evidence-based translational medicine approach with potential rapid entry into pivotal testing and prevention studies

Olivier Sol
Bénédicte Le
Agnes Feige
Jonathan Wagg
Nicolas Fournier
Elena Valatsou
Saskia Delpretti
Julien Rongère
Emma Fiorini
Marija Vukicevic
Julian JG. Gray
Valérie Hliva
Marie Kosco-Vilbois
Johannes Streffer
Andrea Pfeifer

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AC Immune