Biomarker-based development for optimized ACI-24, a novel candidate vaccine for the treatment and prevention of Alzheimer's disease (AD) and AD in Down syndrome

P1-040

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Background

- Amyloid plaques and neurofibrillary tangles are the neuropathologic hallmarks of Alzheimer's disease (AD) with the key constituents being Amyloid Beta (Abeta) and Tau protein, respectively.
- Abeta is a key target for treating AD
- People with Down syndrome (DS) are at increased risk of developing AD like symptoms; 75-100% of people with DS have AD like symptoms by age 60.
- AD associated with DS is a genetic form of dementia, with similar pathophysiology and biomarkers as compared to autosomal dominant AD (ADAD) (Fortea *et al.,* 2021).
- It is apparent that small aggregates such as Abeta oligomers or fragments such as Abeta 1-42 and pyroglutamate Abeta3-42 (pGlu-Abeta3-42) are of key importance for disease initiation with significant implications for translational medicine and success in clinical trial development.

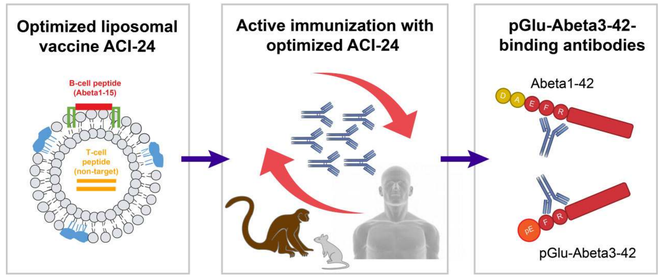

Fig.1: M. Vukicevic et al., Brain Communications, 2022: An amyloid beta vaccine that safely drives immunity to a key pathological species in Alzheimer's disease: pyroglutamate and amyloid beta

Method (ACI – 24)

- ACI-24 is a vaccine targeting Abeta for the treatment and prevention of AD.
- 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.
- Preclinical data have recently demonstrated that a new, optimized formulation of ACI-24 has significantly improved immunogenicity against key toxic species of Abeta including oligomers, Abeta 1-42 and pGlu-Abeta3-42 (Vukicevic et al., 2022; Fig. 1).

Ref:
M. Vukicevic et al., Brain Communications, 2022 Feb 4;4(1) An amyloid beta vaccine that safely drives immunity to a key pathological species in Alzheimer's disease: pyroglutamate and amyloid beta;
J.Fortea et al. Lancet. 2020 Jun 27;395(10242):1988-1997 Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study

ABATE Study

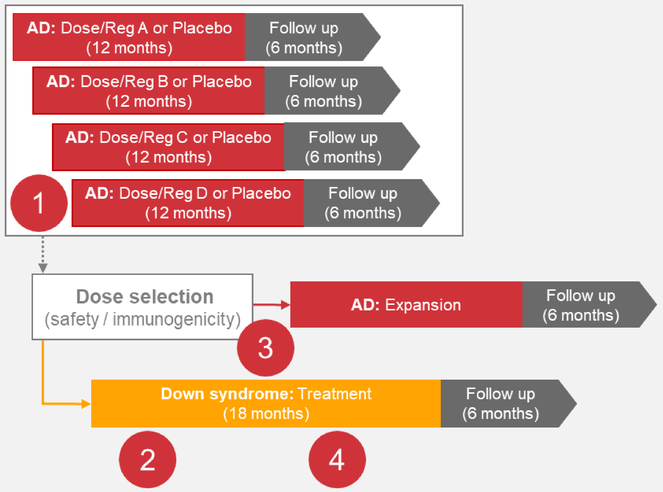

*Fig.3: ABATE Clinical study design, including two study populations (sporadic AD and people with Down syndrome) and two type of interim analyses, based on either safety and antibody titers or pharmacodynamic markers, primarily Amyloid PET. This leads to four distinct decision points **(1)** Safety and Antibody titers in AD, **(2)** Safety and Antibody titers in DS, **(3)** Amyloid PET lowering in AD and **(4)** Amyloid PET lowering in DS. Abbreviations Reg: regimen*

ACI-24 Trial Design

- We present an innovative, translational clinical trial design to understand the immunogenic properties and pharmacodynamic effects of optimized ACI-24 in sporadic AD and in people with DS.
- In both populations, Amyloid PET positivity will be used as a biomarker for study inclusion.
- The design will support the parallel development in subjects with sporadic AD and in subjects with DS.

Interim Analysis – Decision points

- The biomarker-based design, comprising multiple interim analyses, will enable early, and informed decision making, and offers multiple opportunities for acceleration with respect to expansion of the study, initiation of pivotal trials and/or initiation of prevention trials.
- The assessments and following decisions will include early evaluation of safety and antibody titers, the safe transition into the more vulnerable DS population, dose selection based on early and meaningful readouts based on translational biomarkers including Amyloid positron emission tomography (PET) (Fig. 3).
- This will overall de-risk and accelerate development into pivotal study stages.

Alzheimer's disease Clinical Trials

Biomarkers have two main utilities in clinical trials (I) patient selection and stratification and (II) demonstration of pharmacodynamic treatment effects.

I. Biomarkers of Amyloid and Tau are now generally accepted to be core criteria for patient selection in clinical trials, including relevant regulatory guidance "Clinical criteria of eligibility for enrollment in efficacy trials in AD, should be based on current consensus diagnostic criteria. […] The characteristic pathophysiologic changes are typically demonstrated by assessment of various biomarker measures." (Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry, 2018 Draft)

II. Recent clinical trial results in AD, specifically with monoclonal antibodies targeting Abeta, have successfully demonstrated the link between clinical improvements and biomarker improvements, which now can be utilized for future clinical development (Fig. 2).

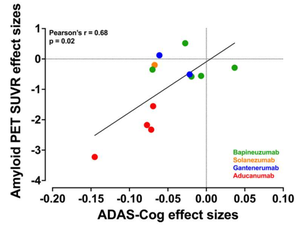

Fig.2: K.I. Avgerinos et al., Ageing Research Reviews, 2021: Effects of monoclonal antibodies against amyloid-β on clinical and biomarker outcomes and adverse event risks: A systematic review and meta-analysis of phase III RCTs in Alzheimer's disease

Conclusions

- The Alzheimer's disease field needs new treatments and innovative clinical trial designs, which will reduce duration of development in an informed way.
- Genetic AD, like ADAD and AD in DS have a high unmet medical need and parallel development with sporadic AD will have key advantages for all populations.
- Safety aspects may be easier and faster demonstrated in sporadic AD, while pharmacodynamic effects are expected to be more homogeneous in genetic AD such as AD in DS.
- Vaccines require less frequent administration compared to monoclonal antibodies or small molecule therapeutics and may provide significant compliance and cost advantages, as such vaccination is a proven approach to managing diseases affecting global populations.
- Biomarker-based translational medicine has been mobilized by the recent understanding of how to clinically evaluate targeting of toxic Abeta fragments and aggregates in trials using monoclonal antibodies.
- These advances allow an innovative trial design for optimized ACI-24 to apply a more efficient evidence-based translational medicine approach and a rapid entry into pivotal testing.