VαcSYn study design – biomarker-based development for ACI-7104.056, a novel candidate vaccine for the treatment and prevention of Parkinson's Disease

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AC Immune 1791

VαcSYn AD/PD 2023 ADVANCES IN SCIENCE & THERAPY March 28 - April 1, 2023 | Gothenburg, Sweden • HYBRID

Background

The aggregation of alpha-synuclein (α-syn) protein into Lewy bodies (LB) and the loss of dopaminergic neurons in the substantia nigra are key pathologic features of Parkinson's disease (PD). Immunotherapies directed against α-syn that aim to reduce the burden of extracellular α-syn aggregates and halt their spread, are promising disease modifying approaches, particularly in early PD stages[1].

- The Parkinson's disease field needs both novel therapies that are disease-modifying and innovative clinical trial designs which could reduce the duration of clinical development in an informed way.
- Vaccines require less frequent administrations compared to monoclonal antibodies or small molecule therapeutics and may provide significant compliance and cost advantages as 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 the targeting of toxic a-syn aggregates in trials using monoclonal antibodies.

Method

ACI-7104.056 is an optimized vaccine formulation targeting α-syn for the treatment and prevention of PD. ACI-7104.056 preferentially targets pathologic α-syn species, including toxic oligomers, the reduction of which has been reported to be associated with signals of clinical benefit[2]. A phase 2 study of ACI-7104.056, denoted VαcSYn, has commenced. The design of the VαcSYn study is data-driven with continuous and early biomarker analyses to inform subsequent development decisions. Biomarker-rich natural history data sets, such as PPMI[a] and data from recent clinical studies of α-syn-directed immunotherapies such as PD01A[b], facilitated selection of relevant biomarkers, potentially predictive of clinical benefit, to inform decision making.

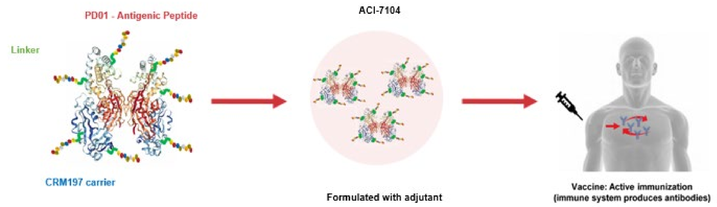


Figure 1: ACI-7104.056 is an optimized vaccine formulation

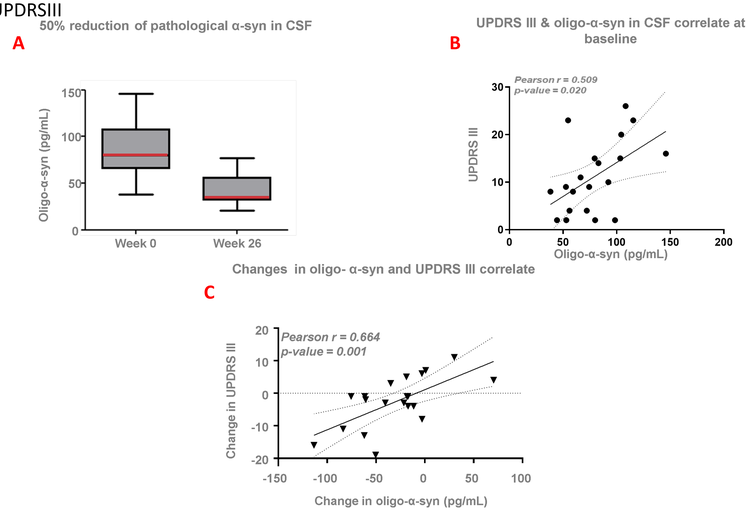
The optimization consists of using CRM197[c] as the carrier protein instead of KLH[d] used in the original formulation vaccine. The antigenic peptide remains the same.

Original formulation vaccine & it's clinical effectiveness[2]

The anti-a-syn original formulation vaccine has been clinically validated:

1. Safe and well tolerated with no safety concerns noted in patients followed for more than 3.5 years
2. Induced strong and boostable antibody responses
3. Evidence of target engagement, 50% reduction in pathological oligomeric α-syn in the CSF (Figure 2A)
4. Signal of clinical efficacy: stabilization of UPDRS III scores correlated with reductions in oligomeric α-syn (Figure 2C)

Figure 2: Oligomeric α-syn (o-α-syn) concentration in CSF at baseline and following treatment with high-dose original formulation vaccine and correlation of o-α-syn with MDS-UPDRSIII



VαcSYn Trial Design & Interim Analyses

We present an innovative, translational clinical trial design to assess the immunogenic properties and pharmacodynamic effects of ACI-7104.056 in early PD. The modelling approaches for this adaptive trial design, comprising multiple interim analyses, will enable early and informed decision making, and offers multiple opportunities for acceleration with respect to expansion of early study cohorts, initiation of pivotal trials and/or initiation of prevention trials.

- **Part 1** designed to assess vaccine safety/tolerability and whether ACI-7104056 vaccine generates robust antibody responses that reduce CSF α-syn oligomer levels.
- **Part 2** designed to assess the clinical response with the objective to de-risk and accelerate development into pivotal study stages. The implementation of meaningful markers like biofluid biomarkers (CSF & blood), advanced MRI, DaTSCAN, and clinical function measured by wearable devices will be also considered in addition to established clinical measures. (Figure 3)

Figure 3: Trial design

VαcSYn trial design power estimates

Data from the PPMI natural history cohort and from the phase 1 clinical study were used to estimate the statistical power of the VαcSYn study design to detect potential ACI-7104.056 treatment effects.

Part 1 design is adequately powered (> 0.80) to detect anti-α-syn IgG responses early to inform dose and scheduling decisions. Likewise, combined cohorts 1 and 2 will allow assessment of additional pharmacodynamic markers to trigger part 2.

Part 2 is designed to detect meaningful effects on clinical measures such as MDS-UPDRS Total Score or markers of disease progression such as mean striatal DaTSCan.

Conclusions

- This Phase 2 study in early PD subjects is based on an innovative two-part trial design to evaluate efficacy of ACI-7104.056 at different levels and thus maintains it's leading position among vaccines targeting α-syn.
- This approach is designed for early de-risking and simultaneously to allow for fast acceleration and enables a rapid entry into a pivotal clinical phase.
- Data science-based assumptions inform timing of interim analyses and will support data interpretation.

Bibliography

1) Volc *et al.*, Lancet Neurol. 2020
2) Zella *et al.*, Neurology and Therapy. 2019

a) PPMI-Parkinson's Progression Markers Initiative
b) PD01A – Vaccine PD01-KLH conjugate
c) CRM197-Cross-Reactive-Material-197 (carrier protein)
d) KLH-Keyhole Limpet Hemocyanin