CLINICAL STUDY PROTOCOL

Including Amendment 4

A Phase Ib Multi-Center, Double-Blind, Randomized, Placebo-Controlled Dose Escalation Study of the Safety, Tolerability and Immunogenicity of ACI-24 in Adults with Down syndrome

Study Number ACI-24-1301

IND Number 15342

CONFIDENTIAL
V5.0 (Final) – 28Jan2020

1 STUDY SYNOPSIS

Study number	ACI-24-1301
IND number	15342
Study Title	A Phase Ib multi-center, double-blind, randomized, placebo-controlled dose escalation study of the safety, tolerability and immunogenicity of ACI-24 in adults with Down syndrome
Coordinating Principal Investigators	**Coordinating Center Principal Investigator** Howard Feldman, MD Alzheimer's Disease Cooperative Study University of California, San Diego 9500 Gilman Drive, MC 0949 La Jolla, CA 92093-0949 United States **Overall Coordinating Principal Investigator** Michael S. Rafii, MD, PhD Alzheimer's Therapeutic Research Institute USC Keck School of Medicine of the University of Southern California 9860 Mesa Rim Road San Diego, CA 92121 United States
Status, Version and Date of Protocol	Final Protocol, version 5.0 dated 28 Jan 2020
Study Planned Dates	FPFV: Q1 2016 LPLV: Q2 2020 (Q1 2021 in case of expansion of the optimal dose cohort)
Number of sites	Approximately 6 sites in United States
Name of the Finished Product	ACI-24
Name of the Active Ingredient	Palmitoylated peptides from the 1-15 sequence β-amyloid peptide (Pal 1-15)
Objectives	**Primary Objectives** To assess the safety and tolerability of ACI-24 in adults with Down syndrome To assess the effect of different doses of ACI-24 on induction of anti-Aβ Ig titer in serum **Secondary Objectives** To explore the efficacy of ACI-24 on Clinical Global Impression of Change (CGIC) in adults with Down syndrome To explore the effect of ACI-24 on cognitive and behavioral endpoints in adults with Down syndrome

	To explore the effect of ACI-24 on whole brain, ventricle and hippocampal volume To explore the effect of ACI-24 on peripheral T cell activation To explore the effect of ACI-24 on putative biomarkers of Alzheimer pathology in Down syndrome including Aβ levels, total tau, phosphorylated tau protein (phospho-tau), NfL, Neurogranin, sAPPα, sAPPß, Orexin-A, inflammatory cytokines, angiogenic proteins and vascular injury markers in plasma and/or in CSF* (*in subgroup) as applicable To assess the effect of different doses of ACI-24 on induction of anti-Aβ Ig titer in CSF* (*in subgroup)
Study Endpoints	**Primary Endpoints** **Safety and tolerability**: Adverse events; global assessment of tolerability; physical and neurological examination; vital signs; suicidal ideation/behavior; MRI imaging; electrocardiogram; routine hematology and biochemistry evaluation in blood and urine; inflammatory markers in blood and CSF **Biological Effect**: Antibody titers (serum anti-Aβ Ig) **Secondary Endpoints** **Efficacy**: Change from baseline in clinical global impression of change; Cognitive function [change from baseline in CANTAB motor control, reaction time, paired associative learning; Brief Praxis Test] and behavior (change from baseline in Vineland Adaptive behavior scale; Neuropsychiatric Inventory) **Biological Effects**: T-cell activation; Biomarkers including Aβ levels, total tau, phospho-tau, NfL, Neurogranin, sAPPα, sAPPß, Orexin-A, inflammatory cytokines, angiogenic proteins and vascular injury markers in plasma and/or in CSF as applicable; Antibody titer (CSF anti-Aβ Ig); **Brain Imaging Effect:** Whole brain, ventricle and hippocampal volume assessed by MRI
Design	This is a prospective placebo controlled, double-blind and randomized dose escalation study of 2 doses of ACI-24 treatment versus placebo over 24 months (12 months treatment phase and 12 months safety follow up period). **Treatment** 2 dose-cohorts of 8 subjects each (6 subjects on ACI-24 300 µg, 6 subjects on ACI-24 1,000 µg and 2 subjects on placebo in each dose-cohort) will be treated with subcutaneous (s.c.) injections at month 0,1,2,3,6,9 and 12 with 12 months follow-up. The dose-cohorts will be studied sequentially in ascending dose order. Safety and tolerability will be reviewed prior to dose escalation. The 2nd dose-cohort is expected to start once safety and tolerability data up through Visit 8 [week 14] of the last subject of the preceding cohort have been reviewed by the DSMB. The number of participants in the optimal dose cohort may optionally be expanded by an additional 8 subjects, leading to a total of 16 subjects in that

	cohort (i.e. 12 subjects on active, 4 subjects on placebo), in order to collect further safety and tolerability data at the corresponding dose. The decision to expand either cohort 1 or cohort 2 will be based on safety, tolerability and immunogenicity or target engagement data after Visit 8 [week 14] of the last subject of cohort 2 - following review of safety and tolerability data by a DSMB. If, based on the interim analysis results at week 14, it is felt more appropriate to collect additional long-term data before deciding whether to expand one of the two cohorts, the decision may be postponed until the time of the interim analysis of data from cohort 2 which is planned at Visit 12 (week 28). **Follow-up** All subjects will be followed up for 12 months after their last dose with a final safety and efficacy assessment.
Number of subjects	Two dose-cohorts of 8 subjects each (6 active, 2 placebo). Total of 16 randomized subjects and an optional expansion of the number of participants in the optimal dose cohort by an additional 8 subjects, totaling 24 randomized subjects (if applicable).
Subject Population	Adults with Down syndrome 25-45 years of age (male and female).
Inclusion/ Exclusion Criteria	**Inclusion criteria** 1. Males or females with Down syndrome aged ≥25 to ≤45 years, with a cytogenetic diagnosis being either Trisomy 21 or Complete Unbalanced Translocation of the Chromosome 21. 2. Subjects and their study partner/legal representative in the opinion of the investigator able to understand and to provide written informed consent. 3. Written informed consent obtained from subjects and their study partner/legal representative before any trial-related activities. 4. In the opinion of the investigator able to fully participate in the trial and sufficiently proficient in English to be capable of reliably completing study assessments. 5. Subjects have a study partner/legal representative who have direct contact with the subjects at least 10 hours per week and who can be asked questions about the subjects. **Exclusion criteria** 1. Subjects weighing less than 40 kg. 2. IQ less than 40 (as assessed by Kaufman Brief Intelligence Test, Second Edition (KBIT-2). 3. In the investigators opinion, any clinically significant current psychiatric or neurologic illness, including a past illness with a risk of recurrence, other than Down syndrome. 4. Any medical condition likely to significantly hamper the evaluation of safety of the study drug. 5. DSM-IV criteria for drug or alcohol abuse or dependence currently met within the past five years.

	6. History or presence of uncontrolled seizures. If history of seizures, they must be well controlled with no occurrence of seizures in the past 2 years prior to study screening. The use of anti-epileptic medications is permitted. 7. History of meningitis or meningoencephalitis. 8. History of malignant neoplasms within 3 years prior to study screening or where there is current evidence of recurrent or metastatic disease. 9. History of persistent cognitive deficits immediately following head trauma. 10. History of inflammatory neurology disorders. 11. History of autoimmune disease with potential for CNS involvement. 12. MRI scan at screening showing a single area of cerebral vasogenic edema, superficial siderosis, or evidence of a prior macro-hemorrhage, or showing more than four cerebral microhemorrhages (regardless of their anatomical location or diagnostic characterization as "possible" or "definite"). 13. MRI examination cannot be done for any reason, including metal implants contraindicated for MRI studies and/or severe claustrophobia. 14. Significant hearing or visual impairment or other issues judged relevant by the investigator preventing to comply with the protocol and to perform the outcome measures. 15. Severe infections or a major surgical operation within 3 months prior to screening. 16. History of chronic or recurrent infections judged to be clinically significant by the investigator. 17. History or presence of immunological or inflammatory conditions which are judged to be clinically significant by the investigator. 18. Celiac disease not on a gluten free diet for at least 3 months prior to study screening. 19. Chronic benign skin pathologies, unless viewed as clinically insignificant in the investigator's opinion. 20. Any vaccine received within the past 2 months before baseline, except influenza vaccine which if indicated must be given at least 2 weeks prior to baseline. 21. Clinically significant arrhythmias or other abnormalities on ECG at screening. (Minor abnormalities documented as clinically insignificant by the investigator will be allowed.) 22. Clinically significant abnormal vital signs including sustained sitting blood pressure greater than 160/90 mmHg. 23. In the opinion of the site investigator, deviations from normal values for hematologic parameters, liver function tests, and other biochemical measures, that are judged to be clinically significant. 24. Subjects with treated hypothyroidism not on a stable dose of medication for at least 3 months prior to screening and having clinically significant abnormal serum T-4 and TSH at screening. 25. Subjects with diabetes mellitus with an HbA1c of ≥ 8.0%. 26. Subjects who have been receiving any experimental drug for Down syndrome with a washout less than 30 days or less than five half-lives of the drug, whichever is longer. 27. Female subjects being pregnant as confirmed by serum testing at screening or planning to be pregnant or lactating.

	28. Female subjects not using a reliable method of contraception (unless abstaining). 29. Patient receiving any anticoagulant drug, or aspirin at doses greater than 100 mg daily in the 7 days prior to lumbar puncture (in order to avoid risk of bleeding during scheduled or unscheduled lumbar puncture) 30. Use of antidepressants other than SSRI/SNRIs at stable dose, antipsychotics (typical or atypical), GABA agonists (e.g. gabapentin), or stimulants (e.g. methylphenidate, modafinil). In exceptional cases, low doses of atypical antipsychotics (e.g. risperidone up to 0.5 mg/day or quetiapine up to 50 mg/day) or benzodiazepines are only allowed after review by the site principal investigator, in consultation with the project director and/or medical monitors. 31. Current use of immunosuppressant or immunomodulating drugs or their use within the past 6 months prior to study screening. Current use of steroids or their use within the past 3 months prior to study screening. 32. Use of Cholinesterase Inhibitor or use of Glutamatergic drugs (Topiramate, Memantine, Lamotrigine) if not on stable dose for at least 3 months prior to screening. 33. Subjects who have donated blood or blood products during the 30 days prior to screening who plan to donate blood while participating in the study or within four weeks after completion of the study.
Study drug	ACI-24 or placebo to be administered subcutaneously
Dosage, duration of treatment	Dose-cohort 1: 300 µg antigen or placebo, dose-cohort 2: 1,000 µg antigen or placebo. In both cohorts, ACI-24 will be administered 7 times: 4 times with 1 month interval, and then 3 times with 3 months interval. The treatment period will last 12 months with the final double-blind evaluation after 24 months (see study plan).

2 STUDY PLAN – INVESTIGATIONAL EVENTS

Study Plan		Treatment Period																		Follow-up Period				
Visit Number	Vs	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	Phone call	V20	Phone call	V21
Time (weeks ± days)	-4w	0 +3d	w2 ±3d	w4 ±3d	w6 ±3d	w8 ±3d	w10 ±3d	w12 ±3d	w14 ±3d	w16 ±3d	w24 ±3d	w26 ±3d	w28 ±3d	w36 ±3d	w38 ±3d	w40 ±3d	w48 ±3d	w50 ±3d	w52 ±3d	w60 ±10d	w66 ±10d	w72 ±10d	w84 ±10d	w96 ±10d
Treatment (Immunization)		•		•		•		•			•			•			•							
Subject Information / Consent	•																							
Medical History, Concomitant Illnesses, Demographic Data	•																							
Inclusion / Exclusion Criteria	•	•*																						
(incl. *KBIT-2* at Vs only)	•																							
Withdrawal Criteria			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant Medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vital signs	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		•		•
Global Assessment of Tolerability			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•					
Physical and neurological examination	•	•	•	•	•	•	•	•	•		•	•		•	•		•	•		•			•	•
CANTAB and BPT	•	•										•						•				•		•
Vineland and NPI		•										•						•				•		•
CGIC (≠ baseline interview)		•≠							•			•			•			•		•		•		•
Suicidal ideation / behavior	•	•																•						•
Lumbar Puncture (CSF) (in subgroup)		•																•						
MRI	•								•			•						•						•
ECG	•											•						•						•
Blood *- Hematology & biochemistry* (incl. CRP & ESR)	•	•	•		•		•		•			•			•			•		•		•		•
- PT (INR)/PTT (only subgroup)	•																•								
- Anti Aß Ig	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		•		•
- Biomarkers		•	•		•		•		•			•			•			•		•		•		•
- T cell profile		•	•						•			•			•			•						
*- TLR4 expression***		•																	•					
- ApoE genotyping *- Screening tests* (see Section 11.1)	•	•																						
Urine																								
- Routine evaluation	•	•	•		•		•		•			•			•			•		•		•		•
- Pregnancy test		•		•		•		•			•			•			•							

* Any results obtained during Screening Visit will be reviewed at Visit 1 [week 0] to ensure that the subject still fulfills Inclusion / Exclusion Criteria. ** TLR4 blood samplings have been collected on site as per the previous versions of the protocol (v1.0 to v4.0) however the TLR4 laboratory testing will not be performed according to clinical study protocol v5.0.