AC Immune

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 LIST OF ABBREVIATIONS

Aβ	β-Amyloid
AD	Alzheimer's Disease
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase
ApoE	Apolipoprotein E
APP	Amyloid Precursor Protein
APPxPS1	Amyloid Precursor Protein x Presenilin-1
ARIA	Amyloid Related Imaging Abnormalities
ARIA-E	Amyloid Related Imaging Abnormalities-Edema/effusions
ARIA-H	Amyloid Related Imaging Abnormalities-Hemosiderin deposition
AST	Aspartate Aminotransferase
BPT	Brief Praxis Test
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CHMP	Committee for Medicinal Products for Human Use
CK	Creatine Kinase
cm (unit)	Centimeter
CRF	Case Report Form
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
C-SSRS	Columbian-Suicide Severity Rating Scale
DS	Down syndrome
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESR	Erythrocyte Sedimentation Rate
ET	Echo Time
FDA	Food and Drug Administration
FLAIR	Fluid Attenuated Inversion Recovery
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GRE	Gradient-Recalled-Echo

HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IUD	Intrauterine Device
IV/IWRS	Interactive Voice/ Interactive Web Response Services
KBIT-2	Kaufman Brief Intelligence Test, Second Edition
kg (unit)	Kilogram
LP	Lumbar Puncture
LPLV	Last Patient Last Visit
µg (unit)	Microgram
mITT	Modified Intention To Treat
MPLA	Monophosphoryl Lipid A
MRI	Magnetic Resonance Imaging
NfL	Neurofilament Light
NPI	Neuropsychiatric Inventory
NOAEL	No Observed Adverse Effect Level
Pal1-15	Palmitoylated peptides from the 1-15 sequence β-amyloid peptide
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate buffered saline
PP	Per Protocol
PD	Protocol Deviation
SAE	Serious Adverse Event
s.c.	Subcutaneous
SD	Standard Deviation
SDV	Source Data Verification
SSRIs	Selective Serotonin Reuptake Inhibitors
SSNIs	Serotonin Norepinephrine Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
sAPP	Soluble Amyloid Precursor Protein

Th1	T helper 1
Th2	T helper 2
TLR	Toll-like receptor
TSH	Thyroid-Stimulating Hormone

2 EMERGENCY CONTACT DETAILS

Medical Advisors:

[redacted]

[redacted]

SAE reporting:

[redacted]

3 PROTOCOL SIGNATURE PAGE

3.1 Sponsor Protocol Signature Page

Chief Scientific Officer:

Medical Director:

Head of Clinical Operations:

Clinical Project Manager:

3.2 Medical Advisor Protocol Signature Page

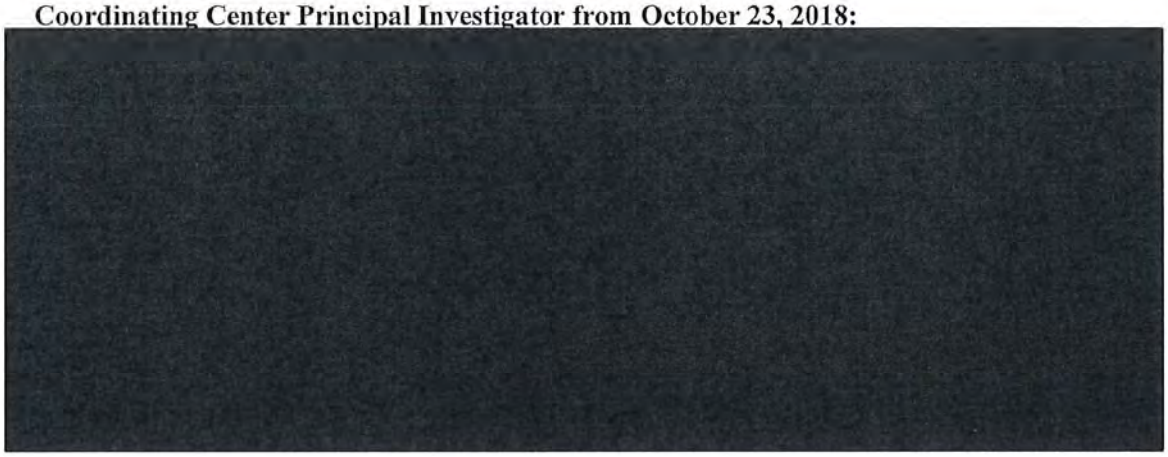
Medical Advisor:

3.3 Biostatistician Study Signature Page

Biostatistician:

3.4 Coordinating Principal Investigators

Coordinating Center Principal Investigator from October 23, 2018:



Overall Coordinating Principal Investigator since the start of the study:

Coordinating Principal Investigator

I agree with the content of the ACI-24-1301 protocol and the nature of the documentation made as part of this study. I have read this protocol, I understand its content and I will work according to this protocol and according to the principles of Good Clinical Practices.

3.5 Site Principal Investigator

Site Principal Investigator

I agree with the content of the ACI-24-1301 protocol and the nature of the documentation made as part of this study. I have read this protocol, I understand its content and I will work according to this protocol and according to the principles of Good Clinical Practices.

Printed Name	Signature	Date

4 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** [redacted] **Overall Coordinating Principal Investigator** [redacted]
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 $\geq$ 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).

5 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 Aβ 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.

6 BACKGROUND INFORMATION

6.1 ACI-24 in Down syndrome (DS)

ACI-24 is an immunotherapeutic vaccine developed for the treatment of β-Amyloid (Aβ) related cognitive decline in Down syndrome (DS) and for the treatment of Alzheimer's disease (AD). ACI-24 consists of a 15-amino acid sequence with complete homology to the human sequence 1-15 of Aβ and hence when injected can be regarded as a therapeutic vaccine for active immunization. The reduction of brain amyloid has been regarded as one of the rational targets for the treatment of Aβ related cognitive decline in DS and AD. Since Aβ, even in its soluble form, is highly neurotoxic, it is believed to play an important role in the pathophysiology of the cognitive impairment of DS people. Treatments reducing the level of Aβ have the potential to modify the progression of cognitive impairment, or can even improve cognitive function. On this basis, ACI-24 is developed as a disease-modifying agent with the aim of producing benefit to subjects without the risks associated with previous immunotherapeutic approaches. A clinical trial of ACI-24 in AD is currently ongoing in Europe. AC Immune now intends to expand the development of ACI-24 to the treatment of subjects affected with Aβ related cognitive decline in DS. All clinical studies, ongoing or planned, are conducted in compliance with Good Clinical Practices (GCP).

DS, or trisomy 21, is caused by an extra copy within the genome of chromosome 21; this chromosome encodes no fewer than 350 genes. The gene of the Amyloid Precursor Protein (APP), which encodes the precursor protein of Aβ, resides on the chromosome 21. In DS people, the entire or at least a part of the chromosome 21 is present in triplicate (Antonarakis *et al.*, 2004). Consequently, this leads to three copies of the gene of the APP further resulting in the generation of an excess of Aβ.

Virtually all people affected with DS show Aβ related neuropathological changes by age 40 (Stanton L.R and Coetzee R.H, 2004). In subjects with DS, Aβ deposits are visible in the cerebral cortex as early as in their 30s (Cenini *et al.*, 2012) (Ikeda *et al.*, 1994).

When studied, the neuropathology of Aβ related cognitive decline in people with DS closely resembles that of AD in persons without DS (Cenini *et al.*, 2012;Lott and Head, 2001;Masters *et al.*, 1985). Autopsy studies of DS people showed that almost all subjects present brain lesions meeting the criteria for AD (Mann *et al.*, 1986) as well as intraneural neurofibrillary tangles, extracellular neuritic plaques, amyloid angiopathy, and deposits of Aβ protein in senile plaques (Hyman, 1992). In people with DS, the Aβ deposits were visible in the cerebral cortex as early as in their 30s (Ikeda *et al.*, 1994). The changes documented, i.e cognitive decline, are identical to those in typical AD. Most people with DS progress to dementia approximately 25 years earlier than those without DS. Other Aβ-dependent changes were observed in plasma or in the Cerebrospinal fluid (CSF) such as axonal injury due to tau or inflammation dependent pathologies and sleep dysregulation due to an altered level of Orexin-A (Mondragon-Rodriguez *et al.*, 2014), (Portelius *et al.*, 2014). There is currently no cure for Aβ related cognitive decline in DS. Current treatments are considered to be mostly symptomatic. There is thus an unmet medical need for more effective treatments for these people.

The development of ACI-24 is based on the hypothesis that if a molecule targets soluble and oligomeric Aβ *in situ*, the molecule can bring clinical benefits to DS people well before the onset of clinically observed dementia by delivering treatments prior to the appearance of severe degenerative changes. In the case of ACI-24, it is anticipated that the antibodies generated by the product will bind to toxic aggregated forms of Aβ, fibrillar deposits and soluble oligomers, to eventually inhibit related toxicity by solubilizing or inhibiting further aggregation. ACI-24 raises polyclonal anti-Aβ antibodies specific to soluble and insoluble aggregated forms including oligomers Aβ which have formed the pathological β-sheet conformation (Hickman *et al.*, 2011). Today, the Aβ oligomers are considered as the most toxic Aβ forms and impairing most cognitive function in AD and in DS people (Teller *et al.*, 1996).

6.1.1 Pharmacology Studies

The currently available pharmacology data were performed with ACI-24 with two different animal species, mice and monkeys, including "proof-of-concept" pharmacology studies in DS mouse model and in APPxPS1 double transgenic mice (these transgenic mice express the human APP and have brain Aβ plaques).

The focus of the non-clinical pharmacological evaluation of ACI-24 was to determine:

- the safety, immunogenicity, and efficacy in mice and monkeys.
- the antibody response induced by different doses of peptide and with different schedules of administration.
- the appropriate route of administration.
- the essential characteristics of its activity that will influence future development.
- the immunogenicity, in particular in a species as close as possible to humans in terms of immune system and disease-models.

For further information, please refer to the most recent version of the Investigator's Brochure.

6.1.2 Toxicology and Safety Studies

The toxicology program consisted of safety and toxicity studies in mice and monkeys. Local tolerance following repeated administrations of ACI-24 was studied during the course of repeat dose toxicity studies in monkeys. The goal of these studies was to evaluate the safety profile of ACI-24 in animal models of APPxPS1 double transgenic mice as well as in non-clinical models following single- and repeat-dose administration.

No safety pharmacology study has been performed with ACI-24, but the vital functions have been monitored in the repeat dose toxicity study in monkey. No pharmacokinetic studies have been performed with ACI-24, as routine studies to assess the ADME profile are neither technically feasible nor meaningful for immunotherapies. The exposure to ACI-24 is assessed by measuring the immune response in pharmacology studies.

For further information, please refer to the most recent version of the Investigator's Brochure.

6.1.3 Clinical Data

To date, ACI-24 demonstrated a favorable tolerability and safety profile in four cohorts of 12 AD patients each (9 on active treatment / 3 on placebo in each cohort) treated with ACI-24 doses of 10 µg (cohort 1), 100 µg (cohort 2), 300 µg (cohort 3) and 1,000 µg (cohort 4) per injection or placebo, in the first-in-man phase 1/2 study in human (study ACI-24-0701).

All 27 AD patients on active treatment in cohorts 1, 2 and 3 in study ACI-24-0701 have completed the treatment period of 7 injections over 48 weeks (first 4 injections with dosing intervals of 4 weeks followed by 3 injections with dosing intervals of 12 weeks). In addition, 4 patients in cohort 3 have received an additional booster injection (ie. a total of 8 injections).

In cohort 4, the first 4 patients have received seven administrations of ACI-24 at a dose of either 1,000 micrograms (3 patients) or placebo (1 patient). One patient has had an additional booster injection (i.e. a total of 8 injections). A further 8 patients have been randomized (6 on active medication, 2 on placebo). One died before receiving the 5th injection, and respectively 4 and 3 patients have received 6 and 7 injections of ACI-24 or placebo.

To date, 2 DS subjects have been randomized in the first cohort of the current ACI-24-1301 study to receive either ACI-24 (300 µg/injection) or placebo. These 2 subjects have received respectively two and six injections of the study drug.

No drug related serious adverse effects were reported to date. There is no indication of meningoencephalitis in the AD patients and DS subjects.

For further information, please refer to the most recent version of the Investigator's Brochure.

6.2 Conclusion

ACI-24 immunization raised significant anti-Aβ specific antibody response in mice and monkeys which was capable of improving memory and to reduce Aβ burden in a DS mouse model. Non-clinical studies in mice confirmed a T-cell independent mechanism of action. Taking this together with ACI-24 also lacking immunodominant T-cell epitopes and with no evidence for inappropriate T-cell activation (Th1) or inflammatory responses, the risk of meningoencephalitis after treatment with ACI-24 is considered to be low. The good preclinical safety profile of ACI-24 was confirmed by the results of toxicology studies performed in mice and monkeys. This positive preclinical profile of ACI-24 is further supported by the ongoing study in patients with AD in Europe (study ACI-24-0701) in which ACI-24 was generally well tolerated and showed no evidence of induction of CNS inflammation to date.

The safety and tolerability of ACI-24, as well as anti Aβ-antibody titers in DS subjects will be investigated in the planned clinical study described below.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

7.1.1 Primary Objectives

- To assess the safety and tolerability of ACI-24 in adults with Down syndrome
- To assess the effect of different doses ACI-24 on induction of anti-Aβ Ig titer in serum

7.1.2 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 ACI-24 on induction of anti-Aβ Ig titer in CSF* (*in subgroup)

7.2 Study Endpoints

7.2.1 Primary Endpoints

Safety and tolerability assessments: 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 assessments: Antibody titer (serum anti-Aβ Ig)

7.2.2 Secondary Endpoints

Efficacy assessments: Change from baseline as measured by 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 assessments: 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 assessment: Whole brain, ventricle and hippocampal volume assessed by MRI

8 STUDY DESIGN AND PROCEDURES

8.1 Study Design

This is a prospective multi-center, placebo controlled, double-blind and randomized study of 2 doses of ACI-24 treatment versus placebo over 24 months.

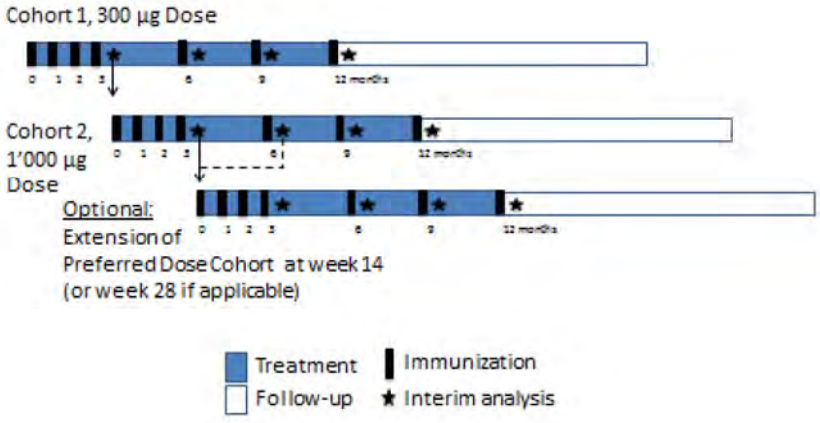
The study consists of 2 dose-cohorts of 8 subjects each (6 subjects on ACI-24 300 µg, 6 subjects on ACI-24 1,000 µg and 2 subjects on placebo in each dose-cohort) with s.c. injections at month 0,1,2,3,6,9 and 12 with 12 months treatment free safety follow-up. The dose-cohorts will be studied sequentially in ascending dose order. 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 Data Safety Monitoring Board (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 optimal dose cohort will be defined as the dose-cohort (either ACI-24 300µg or 1,000µg) showing the best safety, tolerability and immunogenicity or target engagement response profile.

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 get additional long-term data before deciding whether to expand one of the two cohorts, the decision may be postponed until the time of the next interim analysis of cohort 2, which is planned at Visit 12 [week 28]



8.2 Number of Study Sites

The study will be conducted in the United States. Approximately six study sites are planned.

8.3 Study Population

DS subjects have been selected to participate to this study as they virtually all show Aβ-related neuropathological changes by age 40 (Stanton L.R and Coetzee R.H, 2004), however there is currently no cure for Aβ-related cognitive decline in DS although several approaches are currently in clinical development to ameliorate the cognitive impairment.

The age range of DS people in this study will be 25 – 45 years of age. This age range represents DS people at the beginning of developing Aβ plaques and has been chosen as it is now widely accepted in the scientific community of AD disease that an intervention targeting Aβ should occur rather earlier in the disease progress than later. As well, the improvement of cognitive functions in Ts65Dn mice by Aβ lowering therapeutics suggests that Aβ lowering therapies might improve cognitive function also in young DS people. By the age of 40, most DS people have developed Aβ plaque deposits in the brain and most of these individuals develop AD like dementia by the fifth and sixth decade of life (Hyman, 1992) and it is therefore important to include also subjects older than 40 years old.

8.4 Number of Subjects

Two dose-cohorts of 8 subjects each (6 active, 2 placebo). The study anticipates 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). Please refer to the section related to sample size. Additional subjects will possibly be recruited in each cohort to replace subjects withdrawing from the study before the last subject in cohort 1 and 2 have been randomized, respectively.

8.5 Subject Treatment

16 subjects will be randomized with a ratio of 3:1 active (ACI-24) versus placebo (PBS) into 2 dose-cohorts. 8 subjects may additionally be randomized with a ratio of 3:1 active (ACI-24) versus placebo (PBS) into an optional expansion of the optimal dose cohort. Subjects will be administered the study drug 7 times, at month 0,1,2,3,6,9 and 12 with 12 months follow-up. Subjects will receive antigen or placebo via s.c. injection.

The dose–cohorts will be studied sequentially as follows:

- Dose-Cohort 1: 300 µg antigen or placebo
- Dose-Cohort 2: 1,000 µg antigen or placebo

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 after Visit 8 [week 14] of the last subject of the preceding cohort, following review of safety and tolerability by a DSMB.

Within cohorts, there will be an interval of at least one week between first dose administration in the first four subjects in each cohort to detect acute and/or subacute adverse events.

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 get additional long-term data before deciding whether to expand one of the two cohorts, the decision may be postponed until the time of the next interim analysis of cohort 2, which is planned at Visit 12 [week 28].

All subjects will be followed up for 12 months after the last dose with a final safety and efficacy assessment.

8.6 Duration of Trial

8.6.1 Treatment Phase

The period of treatment consists of 4 successive immunizations with 1 month interval, and 3 additional immunizations with 3 months interval. All 7 immunizations consist of the same dose in both cohorts. The overall treatment phase lasts 12 months.

8.6.2 Follow-up Phase

The follow-up in both cohorts lasts 12 months after the last administration.

8.6.3 Study Duration

The study will last approximately 51 months from FPFV to LPLV. The duration of participation for each subject is 25 months (up to 4 weeks between Screening Visit and Visit 1, 24 months from Visit 1 until last visit).

8.6.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Assessment (see section 5).

The end of the study is defined as the last visit of the last subject.

8.7 Rationale for Study Design

The ACI-24-1301 study design makes reference to the first clinical study of ACI-24, study ACI-24-0701, in Alzheimer's disease (AD) subjects. This currently ongoing study includes four cohorts of subjects, treated with a dose of 10 µg (Cohort 1), 100 µg (Cohort 2), 300 µg (Cohort 3) and 1,000 µg (Cohort 4) of ACI-24 or placebo. For more information on patient's exposure to ACI-24, please refer to chapter 6.1.3 clinical data or to the latest version of the Investigator's Brochure.

Furthermore, the good safety profile of ACI-24 is supported by a toxicology study in cynomolgus monkeys with 3 doses of ACI-24 up to the highest dose of 1'320 µg. In this placebo controlled toxicology study, 6 monkeys per group (3M, 3F) were treated with 5 s.c. injections of ACI-24 (doses from 880 µg to 1'320 µg per injection) once every two weeks (over 10 weeks). There were no adverse findings regarding hematology and blood chemistry parameter and no findings on macroscopic investigation. Microscopic investigation of injection site tissue indicated mononuclear cell focus/foci in subcutaneous tissue of minimal to slight intensity and strictly local distribution. All doses up to 1320 µg were considered free of adverse effects.

Given the favorable preclinical and clinical safety profile of higher doses in the study with AD patients, in the present study, the dose level of 300 µg and 1,000 µg is therefore be studied in DS patients.

The study is randomized and placebo controlled to ensure an unbiased and adequate safety and efficacy assessment. The use of placebo as a control is necessary to provide reliable scientific evidence of safety and tolerability and to ensure a reliable evaluation of pharmacologic activity of ACI-24.

Two dose-cohorts of 8 subjects (6 on ACI-24, 2 on placebo in each cohort) will be studied sequentially:

- Cohort 1: ACI-24 (300 µg) or placebo
- Cohort 2: ACI-24 (1,000 µg) or placebo

It is expected that the sample of 16 subjects (12 on active, 4 on placebo treatment) will be sufficient to achieve the main goals of detecting common adverse events and providing information concerning immunogenicity of ACI-24 in this population.

The criterion for starting the 2nd cohort is that the safety data from the previous cohort at Visit 8 [week 14] (3 months of treatment) after review by the DSMB does not indicate a concern which would prevent dose escalation.

The optimal dose cohort will be defined as the dose-cohort (either ACI-24 300µg or 1,000µg) showing the best safety, tolerability and immunogenicity or target engagement response profile.

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 get additional long-term data before deciding whether to expand one of the two cohorts, the decision may be postponed until the time of the next interim analysis of cohort 2, which is planned at Visit 12 [week 28].

8.8 Study Procedures

Subjects will be seen by the investigator at Screening Visit [week -4 to 0] and if eligible, randomized in the study.

The treatment period lasts from Visit 1 [week 0] until Visit 18 [week 52]. The follow-up period includes 3 visits, Visit 19 [week 60], Visit 20 [week 72] and Visit 21 [week 96], with phone calls

in between week 66 and week 84. Within each cohort, the duration of a subject's participation will be up to 25 months (approximately 2 years): up to 4 weeks screening phase, 52 weeks treatment period and 44 weeks follow-up phase.

Study drug is administered at Visit 1 [week 0], Visit 3 [week 4], Visit 5 [week 8], Visit 7 [week 12], Visit 10 [week 24], Visit 13 [week 36] and Visit 16 [week 48]. The subjects are seen 2 weeks after a treatment visit at Visit 2 [week 2], Visit 4 [week 6], Visit 6 [week 10], Visit 8 [week 14] and Visit 11 [week 26], Visit 14 [week 38], Visit 17 [week 50], as well as 4 weeks after a treatment visit at Visit 9 [week 16], Visit 12 [week 28], Visit 15 [week 40] and Visit 18 [week 52].

All study procedures are outlined in the Study Plan. A more detailed description of the study procedures performed at each visit is given in the following sections of the protocol.

The study procedures include:

1) Subject Informed Consent signed at Screening Visit (an Informed Consent must be signed also by the study partner/legal representative)
2) Medical History, Concomitant Illnesses, Demographic Data assessed at Screening Visit
3) Inclusion and Exclusion Criteria, including Kaufman Brief Intelligence Test, Second Edition (KBIT-2) (IQ test) at Screening Visit. Any results obtained during Screening Visit will be reviewed at Visit 1 [week 0] to ensure that the subject still fulfills Inclusion / Exclusion Criteria.
4) Withdrawal Criteria assessed at all visits from Visit 2 [week 2]
5) Concomitant Medication assessed at all visits
6) Adverse Events assessed at all visits (except at Screening Visit)
7) Vital Signs (blood pressure, heart rate, respiratory rate and temperature) assessed at all visits
8) Global Assessment of Tolerability assessed at all visits of the treatment period, from Visit 2 [week 2]
9) Physical and neurological examination assessed at all visits (except at Visit 9 [week 16], Visit 12 [week 28], Visit 15 [week 40] and Visit 18 [week 52])
10) Cognitive assessments (CANTAB, BPT) performed at Screening Visit, Visit 1 [week 0], Visit 11 [week 26], Visit 17 [week 50], Visit 20 [week 72] and Visit 21 [week 96]
11) Scale assessment (Vineland) and Neuropsychiatric Inventory (NPI) performed at Visit 1 [week 0], Visit 11 [week 26], Visit 17 [week 50], Visit 20 [week 72] and Visit 21 [week 96]
12) Clinical Global Impression of Change performed at Visit 1 [week 0], Visit 8 [week 14], Visit 11 [week 26], Visit 14 [week 38], Visit 17 [week 50], Visit 19 [week 60], Visit 20 [week 72] and Visit 21 [week 96]
13) Suicidal ideation/behavior assessed at Screening Visit, Visit 1 [week 0], Visit 17 [week 50] and Visit 21 [week 96]
14) Lumbar puncture (CSF) for assessment of inflammation, antibody titers and biomarkers assessed at Visit 1 [week 0], at least 3 days prior to administration of study drug, and Visit 17 [week 50], only by subjects who did sign a separate Informed Consent for CSF sample collection. Coagulation indices (PT (INR),PTT) must be measured at Screening Visit and Visit 16 [week 48] and results obtained prior to start of the lumbar puncture procedure.

15) MRI Imaging performed at Screening Visit, Visit 8 [week 14], Visit 11 [week 26], Visit 17 [week 50] and Visit 21 [week 96] (performed in a 14 days' timeframe after the Screening Visit date (start of Screening Visit + 14 days) and in a 7 days' timeframe before or after the subsequent visit date (Visit +/- 7 days))
16) ECG performed at Screening Visit, Visit 11 [week 26], Visit 17 [week 50] and Visit 21 [week 96]
17) Blood sampling for:
    - Hematology and biochemistry at Screening Visit, Visit 1 [week 0], Visit 2 [week 2], Visit 4 [week 6], Visit 6 [week 10], Visit 8 [week 14], Visit 11 [week 26], Visit 14 [week 38], Visit 17 [week 50], Visit 19 [week 60], Visit 20 [week 72] and Visit 21 [week 96]
    - Coagulation indices (PT/(INR);PTT) (LP subgroup only) at Screening Visit and Visit 16 [week 48]
    - Anti Aβ Ig at all visits
    - Biomarkers at Visit 1 [week 0], Visit 2 [week 2], Visit 4 [week 6], Visit 6 [week 10], Visit 8 [week 14], Visit 11 [week 26], Visit 14 [week 38], Visit 17 [week 50], Visit 19 [week 60], Visit 20 [week 72] and Visit 21 [week 96])
    - T cell profile Visit 1 [week 0], Visit 2 [week 2], Visit 8 [week 14], Visit 11 [week 26], Visit 14 [week 38] and Visit 17 [week 50]
    - TLR expression at Visit 1 [week 0] and Visit 18 [week 52]
    - ApoE genotyping at Visit 1 [week 0]
    - Screening Tests (see Section 11.1 Screening Tests) at Screening Visit
18) Routine urine evaluation assessed at Screening Visit, Visit 1 [week 0], Visit 2 [week 2], Visit 4 [week 6], Visit 6 [week 10], Visit 8 [week 14], Visit 11 [week 26], Visit 14 [week 38], Visit 17 [week 50], Visit 19 [week 60], Visit 20 [week 72] and Visit 21 [week 96]
19) Urine pregnancy test (for female subjects of childbearing potential) performed before each study drug administration, at Visit 1 [week 0], Visit 3 [week 4], Visit 5 [week 8], Visit 7 [week 12], Visit 10 [week 24], Visit 13 [week 36] and Visit 16 [week 48]
20) Study drug administered at Visit 1 [week 0], Visit 3 [week 4], Visit 5 [week 8], Visit 7 [week 12], Visit 10 [week 24], Visit 13 [week 36] and Visit 16 [week 48]

Study drug administration should be conducted after all other study procedures at each visit have been conducted. Each subject will be observed at the clinical site for 8 hours after the first injection at each dose level during which time subjects will be monitored for vital signs (blood pressure, heart rate, respiratory rate and temperature). Furthermore, each subject will be observed for 4 hours and monitored for vital signs (blood pressure, heart rate, respiratory rate and temperature) on subsequent injections (from 2nd injection on) at each dose level.

Where the burden of all study procedures of a visit are deemed too heavy for the subjects, the visit may be split over two consecutive days. Blood sampling should always be conducted on the first day. Cognitive and clinical rating scales assessments, as well as MRI may be conducted on the second day. Study drug administration should always be conducted after all other study procedures at each visit have been conducted.

During the phone calls at week 66 and week 84, the following study procedures apply:

1) Withdrawal Criteria

2) Concomitant Medication
3) Adverse Events

8.9 Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be designated and will be responsible to monitor/review all study related safety data. The DSMB will consist of experts in the field including DS, neurology and statistics. The DSMB will meet regularly during the study to assess safety data. Safety data of all subjects from all visits will be reviewed by the DSMB at three months interval during the whole study. The DSMB will also meet ad hoc to review safety and tolerability data following Visit 8 [week 14] of the last subject of cohort 1 to provide recommendations on dose escalation, and after Visit 8 [week 14] of the last subject of cohort 2 to provide recommendations on the expansion of one or the other dose-cohort. Unblinded data will be presented to the DSMB. The DSMB will be informed of all SAEs on an ongoing basis, as well as any case of possible encephalitis, with additional meetings held if indicated. The outcome of the DSMB meeting will be registered in minutes and will include a recommendation as to whether to continue the study as planned or to modify or stop the study. The DSMB's full responsibilities and activities are described in a charter.

8.10 Interim Analysis

An interim analysis is planned to be conducted in this study after Visit 8 [week 14] of the last subject of cohort 1 as a basis to allow the dose escalation. The analysis will focus on safety and tolerability. The interim analysis will be conducted in an unblinded fashion - this unblinded data will be presented to the DSMB.

The decision for an optional dose-cohort expansion will be taken on the basis of the data from the interim analysis at Visit 8 [week 14] of the last subject of cohort 2. If, based on the interim analysis results at week 14, it is felt more appropriate to get additional long-term data before deciding whether to expand one of the two cohorts, the decision on an optional dose-cohort expansion may be postponed until the time of the next interim analysis of cohort 2, which is planned at Visit 12 [week 28]. The related interim analyses will be based on safety, tolerability and immunogenicity or target engagement data available in the study at the time of analyses.

In addition to this first interim analysis, safety data of all subjects from all visits will be reviewed by the DSMB at three months interval during the whole study.

Additional interim analyses are planned to be conducted after Visit 9 [week 16], Visit 12 [week 28], Visit 15 [week 40] and Visit 18 [week 52] of the last subject in cohort 1 and in cohort 2 respectively. These analyses will focus on safety, tolerability, antibody titer and inflammatory cytokines data (part of biomarkers). Interim analyses at Visit 12 [week 28] and Visit 18 [week 52] will additionally include biomarkers, as well as CGIC, NPI and Vineland data (part of clinical rating scales and cognitive tests). Since antibody titer and biomarkers are potentially unblinding data, they will be unblinded by group, but blinded as to individual subject numbers – this semi-blinded data will be presented to the sponsor. An interim analysis plan will be prepared and signed before the interim analyses are conducted.

In addition to these interim analyses, biological effects described in section 11.4 will be assessed periodically to gain preliminary information concerning assay functionality and biological effects and to assist in safety assessments as needed.

To prevent unblinding of individual subjects by any potential unblinding data, an external statistician will recode the individual subject numbers as well as allocating the subjects by groups, i.e. active and placebo. Results of the analysis will not be revealed to study monitors or study sites.

9 STUDY POPULATION

9.1 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.

9.2 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 $\geq$ 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 monitor.
31. Current use of immunosuppressant or immunomodulating drugs or their use within the past 6 months prior to study screening. Current use of oral 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.

9.3 Subject Withdrawal

9.3.1 Withdrawal Criteria

A subject should be withdrawn if one of the following applies:

- Use of any investigational drug other than the study drug
- Any significant medical condition which makes completion of the study impossible or seriously hampers the evaluation of safety or efficacy in the study
- Withdrawal of consent by subject or study partner/legal representative. (If the subject or study partner/legal representative withdraws the consent for CSF collection, the subject will be allowed to stay in the study, with the condition that no further lumbar puncture is done for that subject.)
- Pregnancy

The subject may be withdrawn from the trial at the discretion of the Investigator due to safety concerns or incompliance to the protocol. For incompliance to the protocol, efforts should be made to bring the subject back to compliance before withdrawing the subject.

9.3.2 Withdrawal Procedures

Any subject who withdraws from the study prior to completion will be asked to return for a last visit and, if possible, should be examined as per the End of Study Visit (Visit 21). The CRF study completion form must be completed, even if the subject is not able to attend a last visit.

The site personnel will be trained to inform his/her monitor immediately in case of withdrawal.

After withdrawal, subjects should be contacted by phone every 8 weeks (± 10 days) for 12 months after the last vaccine administration (provided any AEs ongoing at the time of withdrawal and any new AEs are resolved or have stabilized after 12 months) and will be asked about resolution of any AEs ongoing at the time of withdrawal and any new AEs.

All data collected from any withdrawn subject may be used in study analyses.

Additional subjects will be possibly recruited to replace subjects withdrawing during the enrollment period of each cohort.

9.4 Study Discontinuation/Early Termination

Should it prove necessary to discontinue the study permanently prior to completion (e.g. compromised safety), each subject should be examined as per the End of Study Visit (Visit 21), if possible. The CRF study completion form must be completed, even if the subject is not able to attend a last visit.

In case it is decided to terminate the study prematurely, the sponsor will immediately notify investigators, relevant authorities and additional contacts. The relevant IRB/IEC will also be informed in a prompt manner. The study product and material will be destroyed or returned as agreed with the sponsor.

10 TREATMENTS

10.1 Study drug

10.1.1 Name and Description

ACI-24 and placebo are sterile liquid formulations supplied in vials. For safety information on ACI-24 please refer to the most recent version of the Investigator's Brochure.

10.1.2 Manufacturing

Study drug will be manufactured by [redacted]

10.1.3 Treatment Administration and Preparation

Because the appearance of the liquid in the vial differs between placebo and ACI-24, a qualified unblinded person will obtain the study product from the pharmacy and administer the study drug (ACI-24 or placebo). The investigator should assign the responsibility of the unblinded dispenser/administrator to a person(s) who will not participate in any subjective evaluation of any study subject. Adverse Events, assessment of causality, CANTAB, BPT, Vineland, NPI, CGIC and Global Assessment of Tolerability are subjective evaluations of study subjects and are, therefore, not permitted to be conducted by the unblinded dispenser/administrator. This permits all other participants to be blinded. Contact between the unblinded dispenser/administrator must not disclose treatment assignment to subject or site staff. The investigator, study coordinator and any study participants other than the unblinded dispenser/administrator must not be allowed to know the study product assigned to any study subject.

The treatment will be administered at the study sites by s.c. injection. For the 300 µg dose, the preferred injection site is the arm, in the fatty tissue over the triceps, alternating between arms for each study drug administration. For the 1,000 µg dose, the preferred injection site is the leg, in the fatty tissue over the anterolateral thigh muscle. For this dose, two injections should be given, the first containing 400 µg and the second containing 600 µg. Both injections should be given into the same leg, with the injection sites in the same area but at least 2.5 cm apart from each other. The injection sites should be alternated between visits, from right leg to left leg.

To administer an equivalent 300 µg or 1,000 µg antigen doses of ACI-24, the following dilution protocol and dose preparation should be followed (A complete product handling instruction manual will be provided to the study site staff responsible for drug administration):

Dose-Cohort 1 (300 µg antigen)

300 µg antigen administration	To administer an equivalent dose of 300 µg antigen, swirl an ACI-24 vial to homogenize. Withdraw 0.75 mL from the vial using a new, sterile 1 mL syringe, wrap in aluminum foil and inject into the arm.
Placebo administration	The placebo is ready-to-use for injection. Swirl an ACI-24 vial to homogenize. Withdraw 0.75 mL from the vial using a new, sterile 1 mL syringe, wrap in aluminum foil and inject into the arm.

Dose-Cohort 2 (1,000 µg antigen)	
1,000 µg antigen administration	To administer an equivalent dose of 1,000 µg antigen, swirl three ACI-24 vials to homogenize. Withdraw 1.0 mL from one vial using a sterile 1 mL syringe. Withdraw 1.0 mL from the second vial using a new sterile 2 mL syringe. Withdraw 0.5 mL from a third vial using the same sterile 2 mL syringe. The second syringe now contains 1.5 mL. Wrap both syringes in aluminum foil and inject the contents of the two syringes into the fatty tissue over the anterolateral thigh muscle of the same leg, with the injection sites in the same area but at least 2.5 cm from each other.
Placebo administration	The placebo is ready-to-use for injection. Swirl three ACI-24 vials to homogenize. Withdraw 1.0 mL from one vial using a new, sterile 1 mL syringe. Withdraw 1.0 mL from the second vial using a new sterile 2 mL syringe. Withdraw 0.5 mL from a third vial using the same sterile 2 mL syringe. The second syringe now contains 1.5 mL. Wrap both syringes in aluminum foil and inject the contents of the two syringes into the fatty tissue over the anterolateral thigh muscle of the same leg, with the injection sites in the same area but at least 2.5 cm from each other.

Study drug administration should be conducted after all other study procedures at each visit have been conducted. Each subject will be observed at the clinical site for 8 hours after the first injection at each dose level. Before the first injection, and then after 1 hour, 2 hours, 4 hours, 6 hours and 8 hours, subjects will be monitored for vital signs (blood pressure, heart rate, respiratory rate and temperature). Furthermore, each subject will be observed for 4 hours and monitored for vital signs before the first injection, and then after 1 hour, 2 hours, 4 hours (blood pressure, heart rate, respiratory rate and temperature) on subsequent injections (from 2nd injection on) at each dose level.

10.1.4 Packaging and Labeling

The vials of all study drug will be primarily labeled at the manufacturer [redacted] The primary vials will be sent to the final drug distributor that will be responsible for the final study specific labeling, packaging and site dispatching.

10.1.5 Distribution and Storage

The vials will be supplied to the pharmacy of the study site after the study has been approved by the IRB/IEC and FDA.

The unblinded site staff appointed to administer the product will receive the appropriate vial - each vial carries a study drug number (see randomization and blinding procedure, 10.2 and 10.3) and proceeds with subject treatment. The empty vial will be returned to the pharmacy.

The study products should be stored refrigerated at 2-8°C. The investigator/pharmacist agrees not to distribute the test articles to anyone, except to the appointed person who is responsible for administering the product. This person agrees not to administer the products to anyone, except to the subjects participating in this study. Study products must be stored as indicated. Any deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the study products must be quarantined and not used until the sponsor provides documentation of permission to use the study products.

Used and unused vials remaining at completion of the study should be returned via the sponsor's representative (e.g. monitor) or the sponsor can arrange with the clinic for it to be destroyed onsite with a proper certification of destruction.

10.1.6 Accountability and Reconciliation

A product accountability form will be used by the pharmacist/independent unblinded qualified person responsible for the injection. Used vials will be kept during the study for accountability until they have been verified by the unblinded monitor. Once drug accountability has been verified, used vials may be returned to study drug supplier with approval from the Sponsor. All study vials (investigational product and placebo) received and dispensed throughout the trial period will be inventoried and accounted for the trial period by the unblinded qualified person on the corresponding "product accountability form". The Principal Investigator is accountable for all the study products supplied by the sponsor.

10.2 Randomization

A randomization list based on a sequence of random numbers, and individual study drug codes will be computer generated. Study drug will be labeled with the corresponding study drug number. Investigators will use a secure web-based system to randomize eligible subjects to study drug. Additionally, this system will be programmed to ensure that the randomization of the first 4 subjects, of each dose level, are kept in an interval of more or equal (≥) than 7 days. Specific instructions for the use of the system will be provided to the participating sites.

10.3 Blinding Procedure

The study is blinded to study subjects and site personnel, except to the unblinded qualified person administrating the product. The pharmacist is also unblinded. The investigator and subject will remain blinded to subject treatment throughout the study, unless an emergency unblinding at the site becomes necessary because of a subject AE.

The Principal Investigator will be provided the site specific unblinded list after study database lock. It is the Principal Investigators' responsibility to decide whether this information should or should not be shared with the subjects.

In order to remain blinded, raters performing the psychometric tests should not have access to any clinical assessment data (e.g. medical assessments, adverse events).

A set of sealed envelopes with study drug number identification will be made available at pharmacy/site to be opened only when medically indicated in an emergency.

10.4 Unblinding Procedure

In emergency circumstances where the investigator identifies an urgent clinical need to know whether the subject is receiving active study drug or placebo, the code break envelopes may be used by the investigator/pharmacist directly. In such cases the rationale must be documented on the corresponding envelope, with immediate notification of the monitor and sponsor clinical project manager.

The code break will also be reported in the subject specific CRF and events leading to the emergency breaking will be recorded in the serious adverse event (SAE) report form. All envelopes will be retrieved at the end of the study.

10.5 Concomitant Medications

10.5.1 Permitted Medications

During the course of the trial, subjects may receive the prescribed medications and treatments as indicated by their clinical condition given that dosing wherever possible is stable throughout the study period. Over the counter drugs (e.g. vitamins, acetaminophen/paracetamol) are permitted. All medications and treatments must be documented in the concomitant medication section of the case report forms and on the patient diary. Any change in current medication (e.g. doses), must be discussed first with study investigators.

The dose of acetylcholinesterase inhibitor should remain stable during the study whenever possible.

10.5.2 Unauthorized Medications

The following treatments are not permitted throughout the study (Please see the next section for Permitted Medications Under Certain Circumstances):

- Anticoagulant therapy or aspirin above 100 mg daily (intermittent use of aspirin at higher doses is allowed if the maximum daily dose does not exceed 100 mg daily in the 7 days prior to lumbar puncture)
- Antidepressant other than SSRI/SNRIs at stable dose
- Antipsychotics (typical)
- GABA agonists (e.g. gabapentin)
- Stimulants (e.g. methylphenidate, modafinil)
- Oral steroids

- Immunosuppressant or immunomodulating drugs
- Vaccinations other than influenza vaccine (see section 10.5.3) which, if indicated, should be given at least 2 months prior to baseline or if required after baseline at least two weeks before the study drug has been given

10.5.3 Permitted Medications Under Certain Circumstances

The following treatments are permitted in the study as clinically indicated:

- Cholinesterase inhibitors and/or glutamatergic drugs (Topiramate, Memantine, Lamotrigine): The dose of acetylcholinesterase inhibitor and/or glutamatergic drugs should remain stable during the study whenever possible. Treatment initiation or dose changes during the study should be discussed with the medical monitor whenever possible.
- Short courses of corticosteroids if clinically indicated, e.g. for asthma exacerbations
- Influenza vaccine, if indicated, should be given at least 2 weeks prior to baseline or wherever possible at least 2 weeks before any individual dose of ACI-24 or placebo.
- 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 monitor.

10.5.4 Prior Medications

All relevant medications received by the subject within 30 days before the Screening Visit will be recorded. Over the counter drugs (e.g. vitamins, acetaminophen/paracetemol) taken by the subject within 14 days before Screening Visit will be recorded.

11 STUDY ASSESSMENTS

11.1 Screening Tests

The following tests will be measured at Screening Visit only:

- Vitamin B12
- Thyroid function tests (T4, T3, TSH)
- HIV screening
- Syphilis serology
- Hepatitis B and Hepatitis C
- Serum pregnancy test: Beta-HCG pregnancy tests will be carried-out in women of child bearing potential. On the following visits, pregnancy test strips to be dipped into the urine will be performed.

11.2 ApoE Genotyping

Blood for ApoE genotyping will be collected at Visit 1 (Baseline).

11.3 Safety Assessments

11.3.1 Adverse Events

Adverse events will be assessed as described in Section 13, Safety Procedures.

11.3.2 Global Assessment of Tolerability

From Visit 2 to Visit 18 (inclusive), the study physician will be asked to make a global assessment of the tolerability of the study product as follows:

- Very Good
- Good
- Moderate
- Poor

11.3.3 Physical and Neurological Examination

Weight will be recorded in kg and height in cm.

Physical examination will include assessment of the head, eyes, ears, nose, throat, heart, chest, lungs, abdomen, extremities, peripheral pulses, skin and any other physical conditions of note.

The neurological examination will include examination of the cranial nerves, upper and lower extremities for muscle strength, reflexes, sensation and cerebellar function.

11.3.4 Vital Signs

Blood pressure will be measured in the sitting and standing positions at Screening Visit and Visit 1 (Baseline). The sitting blood pressure should be measured first and should be measured after

the subject has been sitting down for 5 minutes. The subject should then be asked to stand and the standing blood pressure should be measured after the subject has been standing for 2 minutes. At all other visits, blood pressure will be measured in the sitting position only.

At Visit 1, vital signs should also be measured in the sitting position before the injection, and then after 1 hour, 2 hours, 4 hours, 6 hours and 8 hours. At Visit 3, Visit 5, Visit 7, Visit 10, Visit 13 and Visit 16, vital signs should be measured in the sitting position before the injection, and then after 1 hour, 2 hours, and 4 hours.

Blood pressure will be measured with a standardized manometer; alternative validated methods of measurement may also be used. The point of disappearance of Korotkoff sounds (phase V) will be recorded as the diastolic blood pressure where a sphygmomanometer is used.

The same arm should not be used for blood collection and blood pressure assessments if possible. If there is a clinically important change in blood pressure from the previous reading, measurements will be repeated immediately to confirm the change.

Heart rate will be determined over 60 seconds following the recording of blood pressure in the corresponding position.

Body temperature will be measured and recorded. Measurement can be taken by either oral or tympanic methods.

Respiratory rate will be measured at rest by observation.

11.3.5 Magnetic Resonance Imaging (MRI)

MRI scans will be conducted at Screening Visit [week -4 to 0], Visit 8 [week 14], Visit 11 [week 26], Visit 17 [week 50] and Visit 21 [week 96] (MRI scan can be performed in a 14 days' timeframe after the Screening Visit date (start of Screening Visit + 14 days) and in a 7 days' timeframe before or after the subsequent visit date (Visit +/- 7 days)). For the Screening Visit, MRI scan should be performed as close as possible to this visit in order to confirm the patient eligibility. Scans will be systematically analyzed for the presence of encephalitis, micro hemorrhages, superficial siderosis or vasogenic edema.

Scanners will be of 1.5T/3T and will be monitored regularly with phantom quality checks.

A standard acquisition protocol will be used by all sites and detailed in a separate manual. This will include amongst others T2*-weighted gradient-recalled-echo (GRE) sequences (coronal, 3-mm slice thickness, 1mm in-plane resolution; Echo Time (TE) of 20ms or greater) and a fast fluid-attenuated inversion recovery (FLAIR) sequence (axial, 5-mm contiguous slice, 1mm-in plane resolution).

11.3.6 Safety Blood and Urine Analysis

Measurement tests for safety blood and urine analysis will be analyzed at a central laboratory. Details regarding handling, storage and shipment of the safety blood and urine samples will be provided to the study centers in a Laboratory Manual.

11.3.6.1 Safety Blood Analysis

Safety hematological analysis will be done at visits indicated in the study plan (section 5) and will include:

- red blood cell count
- hemoglobin
- hematocrit
- red cell indices
- white blood cell count, including differential
- platelet count

Blood for analysis of Coagulation indices (PT (INR)/PTT) (LP subgroup only) will be drawn at Screening Visit [week -4 to 0] and V16 [week 48]. Results must be obtained prior to start of the lumbar puncture procedure.

Safety biochemistry will be done at visits indicated in the study plan (section 5). Analyses will include:

- sodium
- potassium
- chloride
- urea
- creatinine
- calcium
- inorganic phosphate
- glucose
- total bilirubin
- total protein
- albumin
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- alkaline phosphatase
- gamma GT
- creatine kinase (CK)
  cholesterol
- triglycerides
- uric acid

If the blood sample could not be taken at any visit, it should be taken at the next possible visit.

11.3.6.2 Safety Urine Analysis

Safety urine analysis will be done at visits indicated in the study plan (section 5). Analyses will include:

- pH
- protein
- glucose
- ketones
- blood

If the urine sample could not be taken at any visit, it should be taken at the next possible visit.

11.3.7 Inflammatory Markers in Blood and CSF

11.3.7.1 Blood

CRP and ESR will be measured at the same visits as the routine Biochemistry evaluation. ESR will be performed locally.

If the blood sample could not be taken at any visit, it should be taken at the next possible visit.

11.3.7.2 CSF

CSF samples will be collected in a subgroup of subjects who have signed a separate informed consent allowing the collection of CSF samples. CSF samples of this subgroup of subjects obtained by lumbar puncture at Baseline Visit [week 0], at least 3 days prior to administration of study drug, and Visit 17 [weeks 50] will be examined for evidence of inflammation including:

- Protein
- CSF/serum albumin ratio
- IgG index
- Oligoclonal bands
- Glucose levels
- Differential Cell Count (performed at the local site laboratory)

If the CSF sample could not be taken at any visit, it should be taken at the next possible visit.

11.3.8 Electrocardiogram (ECG)

12-lead ECG recordings are required and must be examined for abnormalities locally. Printouts of each ECG must be kept at the site for archiving and should include information about the paper speed, voltage calibration, lead identification for each lead, trial number, subjects' CRF number and date of birth, date and time of recording and investigator's dated signature. All data will be transferred to a central laboratory for manual measurement of selected intervals and assessment. A manual describing all methods for collecting data will be provided to the Investigator.

11.3.9 Suicidal Ideation/Behavior

At Screening Visit [week -4 to 0], Visit 1 [week 0], Visit 17 [week 50] and Visit 21 [week 96], the study partner/legal representative and the subject will be asked the questions related to suicidal ideation and suicidal behavior:

1) Has the subject indicated that they wished they would die or sleep and never wake up? (suicidal ideation)

2) Has the subject attempted suicide? (suicidal behavior)

3) Has the subject harmed himself/herself? (suicidal behavior)

4) Has there been self-injurious behavior? (suicidal behavior)

If the answer to any of these questions is yes, then the investigator will further evaluate with the Columbian-Suicide Severity Rating Scale (C-SSRS).

11.4 Biological Effect Assessments

Samples will be assessed periodically to gain preliminary information concerning assay functionality and biological effects and to assist in safety assessment as needed.

11.4.1 Anti-Aβ Ig Titer

At all visits, blood will be collected for determination of anti-Aβ Ig titer (Aβ1-42). If the blood sample could not be taken at any visit, it should be taken at the next possible visit.

If the number of CSF samples is sufficient, anti-Aβ Ig titer (Aβ1-42) will be analyzed from CSF collected at Visit 1 [week 0] and Visit 17 [week 50]. If CSF could not be collected at any visit, it should be taken at the next possible visit, if possible.

11.4.2 Blood T-cell Activation

Blood will be collected for determination of T-cell activation (IFN-γ and IL-4) in PBMC at Visit 1 [week 0], Visit 2 [week 2], Visit 8 [week 14] and Visit 11 [week 26], Visit 14 [week 38], Visit 17 [week 50]. If blood could not be collected at any visit, it should be taken at the next possible visit, if possible.

11.4.3 TLR4 Expression

Blood will be collected for determination of TLR4 expression in PBMC at Visit 1 [week 0] and at Visit 18 [week 52]. If blood could not be collected at any visit, it should be taken at the next possible visit, if possible.

11.4.4 Biomarkers in CSF and Plasma

The following biomarkers will be assessed in CSF and/or in plasma as applicable:

- Aβ levels such as Aβ1-42, Aβ1-40, Aβ1-38
- Total tau, phospho-tau
- NfL
- Neurogranin
- sAPPα, sAPPβ
- Orexin A
- Inflammatory cytokines
- Angiogenic proteins
  Angiogenic proteins such as VEGF-D, PIGF and VEGFR1 will be assessed.
- Vascular injury markers
  Vascular injury markers such as VCAM-1 will be assessed.

11.5 Brain Imaging Effect Assessments

11.5.1 Magnetic Resonance Imaging (MRI)

MRI scans will be conducted at Screening Visit [week -4 to 0], Visit 8 [week 14], Visit 11 [week 26], Visit 17 [week 50] and Visit 21 [week 96] (MRI scan can be performed in a 14 days'

timeframe after the Screening Visit date (start of Screening Visit + 14 days) and in a 7 days' timeframe before or after the subsequent visit date (Visit +/- 7 days)).

Serial measurement of whole brain, ventricle and hippocampal volume will be conducted using MRI to allow assessment of the rate of whole brain and hippocampal atrophy.

Precise acquisition protocols will be detailed in an MRI acquisition manual, with all sites receiving training on this prior to the commencement of the study.

Scans will be analyzed centrally; the scans will also be examined locally.

11.6 Efficacy Assessments

11.6.1 Clinical Rating Scale Assessments

The clinical rating scales should be performed by a trained clinical rater (experienced site personnel). The clinical rater should not perform or review the results of the psychometric tests.

Whenever possible the clinical rating scales of a subject should be performed by the same clinical rater throughout the study. An experienced and adequately trained back-up rater is recommended.

Whenever possible the clinical rating scales should be performed at the same time of day throughout the study for each individual subject.

11.6.1.1 Clinical Global Impression of Change Scale

The Clinical Global Impression of Change scale (CGIC) is a 7 point scale that requires the clinician to assess how much the subject's illness has improved or worsened relative to a baseline state at the beginning of the intervention. This 7 point scale is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

11.6.1.2 Vineland-II Adaptive Behavior Scale (VABS-II)

The Vineland-II Adaptive Behavior Scale (VABS-II) interview form administered to the study partner/legal representative will measure personal and social skills such as communication, daily living skills, and socialization and will provide a composite score reflecting an individual's overall function. In addition, the optional maladaptive behavior index could also be used. The survey interview form will be used and administered to the study partner/ legal representative using a semi-structured interview format.

11.6.1.3 Neuropsychiatric Inventory (NPI)

The NPI is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on interview with the study partner (Cummings *et al.*, 1994). The NPI evaluates both the frequency and severity of 12 neuropsychiatric disturbances. Frequency assessments range from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously) as well as severity (1=mild, 2=moderate, 3=severe). The overall score and the score for each subscale are the product of severity and frequency.

11.6.2 Cognitive Assessments

The cognitive assessments should be performed by a trained independent rater (psychologist or by another site personnel experienced on psychometric tests). The cognitive rater should neither perform nor have access to any subject clinical assessments throughout the study, and should not perform the clinical rating scales described under section 11.6.1.

Whenever possible the cognitive assessments of an individual subject should be performed by the same cognitive rater throughout the study. An experienced and adequately trained back-up rater is recommended.

Whenever possible the cognitive tests should be performed at the same time of day throughout the study for each individual subject.

11.6.2.1 Kaufman Brief Intelligence Test, Second Edition (KBIT-2)

The Kaufman Brief Intelligence Test, Second Edition (KBIT-2) will calculate the intelligence quotient and is an individually-administered assessment of intellectual ability normed for ages 4 – 89 years. Both verbal ability and nonverbal reasoning ability are assessed. The Verbal scale includes two subtests: Verbal Knowledge, which measures receptive vocabulary and general knowledge about the world; and Riddles, which measures primarily expressive reasoning. The Nonverbal scale (Matrices) measures nonverbal matrix reasoning, that is, understanding of relations between either concrete stimuli (pictures of objects) or abstract stimuli (e.g., designs or symbols). The KBIT-2 yields a Verbal SS, a Nonverbal SS, and a Composite IQ based on performance on the Verbal and Nonverbal scales. Each of these has a general- population mean of 100, SD of 15, and range from 40 – 160. According to the KBIT-2 manual, internal consistency reliability for children aged 4 – 18 years was .90 for the Verbal scale, .86 for the Nonverbal scale, and .92 for IQ Composite. Adjusted test-retest reliability for ages 4 – 12 years was .88 for the Verbal scale, .76 for the Nonverbal scale, and .88 for IQ Composite. Reliability was slightly higher for ages 13 – 21 years. No significant sex differences were reported for Verbal SS or IQ Composite.

11.6.2.2 Cambridge Neuropsychological Test Automated Battery (CANTAB)

The Cambridge Neuropsychological Test Automated Battery (CANTAB) can be used to assess cognition in the study. The CANTAB is a computerized assessment of neuropsychological function composed of a number of tests. The tests selected from this battery for this study are as follows:

Motor control (MOT): The subject is asked upon appearance of a cross on the screen, to touch it as quickly and accurately as possible using the index finger of their dominant hand. This is essentially a practice routine to get skilled with regards to touchscreen use. The outcome parameter is median reaction time.

Reaction time (RTI): The subject is asked to hold the index finger on the holding button on the button box and keep it pressed until 1 of the 5 circles on the screen lights up and then touch that circle with the index finger as quickly and accurately as possible. In the Simple condition, the middle of the five circles lights up (Simple Reaction Time). In the 5-choice condition, any of the 5 circles can light up (5-Choice Reaction Time).

Paired associated learning (PAL): The subject is shown 2-8 (max) distinct visual patterns, each on 1 of 8 positions of an octagon on the screen. The task is to memorize which pattern occurred where. After the memorization stage, each pattern is shown in the center of the screen and then the subject has to touch 1 of 8 possible positions where the pattern first occurred.

A maximum of 30 minutes are foreseen to administer these 3 tests.

11.6.2.3 Brief Praxis Test (BPT)

The Brief Praxis Test (BPT), a modification of the Dyspraxia Scale for Adults with Down syndrome, is analogous to the Severe Impairment Battery. The original Dyspraxia Scale was a 62-item scale evolved from the Home Behavioral Assessment, and had been shown to capture deterioration among persons with DS in the early stage of dementia of the Alzheimer's type. The BPT consists of 20 items selected from the larger scale because they showed maximum change over a 3-years period among adults with DS. The test can be administered in 30 min or less, and requires simple behavioral responses with minimal language demands. Items are readily recorded and scored. It has been validated in a clinical trial of vitamin E in DS as a primary outcome measure (Petersen *et al.*, 2005).

12 SCHEDULE OF ASSESSMENTS

Vs-Screening [week -4 to 0]

- Written informed consent from the subject and from the study partner/legal representative (for participation in the study, both the subject and the authorized representative must sign the inform consent)
- Written informed consent to allow lumbar puncture from the subject and from the study partner/legal representative: this additional informed consent should be signed only if the subject agrees that CSF samples are collected
- Inclusion and exclusion criteria (incl. KBIT-2)
- Medical History, Concomitant Illnesses and Demographic Data
- Concomitant Medication
- Vital signs
- Physical and neurological examination
- CANTAB
- BPT
- Suicidal ideation/behavior
- MRI (Safety and whole brain and hippocampal volume) (performed in a 14 days' timeframe after the visit date (start of Screening Visit + 14 days))
- ECG
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Coagulation indices assessment (this analysis will be done only for subjects in whom CSF samples are collected and results must be obtained prior to start of the lumbar puncture procedure)
  - Screening tests (see Section 11.1 Screening Tests): Vitamin B12, thyroid function tests, HIV, Syphilis, Hepatitis B and C, pregnancy test
- Routine urine evaluation

Visit 1/ Baseline [week 0]

This visit should take place within a period of up to 4 weeks + 3 days after Screening Visit (Vs).

- Any results obtained during Screening Visit (KBIT-2, central MRI readings, central ECG readings, blood and urine tests) will be reviewed at Visit 1 [week 0] to ensure that the subject still fulfills Inclusion / Exclusion Criteria.
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Physical and neurological examination
- CANTAB
- BPT
- Vineland
- NPI

- CGIC baseline interview
- Suicidal ideation/behavior
- Lumbar puncture (8-20 ml): only for subjects who signed the informed consent for CSF collection (performed after results of coagulation indices have been received and at least 3 days prior to administration of study drug)
- Blood sample, collected for:
    - Routine hematology and biochemistry
    - Anti-Aβ Ig titers (Aβ1-42)
    - Biomarker assessment
    - T cell profile assessment
    - TLR4 expression
    - ApoE genotyping
- Routine urine evaluation
- Urine pregnancy test
- Administration of study drug

Visit 2 [week 2]

This visit should take place 2 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
    - Routine hematology and biochemistry
    - Anti-Aβ Ig titers (Aβ1-42)
    - Biomarker assessment
    - T cell profile assessment
- Routine urine evaluation

Visit 3 [week 4]

This visit should take place 4 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
    - Anti-Aβ Ig titers (Aβ1-42)
- Urine pregnancy test
- Administration of study drug

Visit 4 [week 6]

This visit should take place 6 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Biomarker assessment
- Routine urine evaluation

Visit 5 [week 8]

This visit should take place 8 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)
- Urine pregnancy test
- Administration of study drug

Visit 6 [week 10]

This visit should take place 10 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Biomarker assessment
- Routine urine evaluation

Visit 7 [week 12]

This visit should take place 12 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)
- Urine pregnancy test
- Administration of study drug

Visit 8 [week 14]

This visit should take place 14 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- CGIC
- MRI (Safety and whole brain and hippocampal volume) (performed in a 7 days' timeframe before or after the visit date (Visit +/- 7 days))
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Biomarker assessment
  - T cell profile assessment
- Routine urine evaluation

Visit 9 [week 16]

This visit should take place 16 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)

Visit 10 [week 24]

This visit should take place 24 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)
- Urine pregnancy test
- Administration of study drug

Visit 11 [week 26]

This visit should take place 26 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- CANTAB
- BPT
- Vineland
- NPI
- CGIC
- MRI (Safety and whole brain and hippocampal volume) (performed in a 7 days' timeframe before or after the visit date (Visit +/- 7 days))
- ECG
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Biomarker assessment
  - T cell profile assessment
- Routine urine evaluation

Visit 12 [week 28]

This visit should take place 28 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs

- Global Assessment of Tolerability
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)

Visit 13 [week 36]

This visit should take place 36 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)
- Urine pregnancy test
- Administration of study drug

Visit 14 [week 38]

This visit should take place 38 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- CGIC
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Biomarker assessment
  - T cell profile assessment
- Routine urine evaluation

Visit 15 [week 40]

This visit should take place 40 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)

Visit 16 [week 48]

This visit should take place 48 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)
  - Coagulation indices assessment (this analysis will be done only for subjects whom CSF samples are collected and results must be obtained prior to start of the lumbar puncture procedure)
- Urine pregnancy test
- Administration of study drug

Visit 17 [week 50]

This visit should take place 50 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Physical and neurological examination
- CANTAB
- BPT
- Vineland
- NPI
- CGIC
- Suicidal ideation/behavior
- Lumbar puncture (8-20 ml): only for subjects who signed the informed consent for CSF collection (performed after results of coagulation indices have been received)
- MRI (Safety and whole brain and hippocampal volume) (performed in a 7 days' timeframe before or after the visit date (Visit +/- 7 days))
- ECG
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Biomarker assessment
  - T cell profile assessment
- Routine urine evaluation

Visit 18 [week 52] (End of treatment visit)

This visit should take place 52 weeks ± 3 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Global Assessment of Tolerability
- Blood sample, collected for:
  - Anti-Aβ Ig titers (Aβ1-42)
  - TLR4 expression

Visit 19 [week 60]

This visit should take place 60 weeks ± 10 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Physical and neurological examination
- CGIC
- Blood sample, collected for:
  - Routine hematology and biochemistry
  - Anti-Aβ Ig titers (Aβ1-42)
  - Biomarker assessment
- Routine urine evaluation

Phone call 1 [week 66]

This phone call should take place 66 weeks ± 10 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events

Visit 20 [week 72]

This visit should take place 72 weeks ± 10 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Physical and neurological examination
- CANTAB
- BPT
- Vineland

- NPI
- CGIC
- Blood sample, collected for:
    - Routine hematology and biochemistry
    - Anti-Aβ Ig titers (Aβ1-42)
    - Biomarker assessment
- Routine urine evaluation

Phone call 2 [week 84]

This phone call should take place 84 weeks ± 10 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events

Visit 21 [week 96] (End of study visit)

This visit should take place 96 weeks ± 10 days after Visit 1.

- Withdrawal criteria
- Concomitant medication (describe new and/or changes from the previous visit)
- Adverse events
- Vital signs
- Physical and neurological examination
- CANTAB
- BPT
- Vineland
- NPI
- CGIC
- Suicidal ideation/behavior
- MRI (Safety and whole brain and hippocampal volume) (performed in a 7 days' timeframe before or after the visit date)
- ECG
- Blood sample, collected for:
    - Routine hematology and biochemistry
    - Anti-Aβ Ig titers (Aβ1-42)
    - Biomarker assessment
- Routine urine evaluation

Unscheduled Visit (UV)

Any subject who undergoes an unscheduled visit should be investigated according to best clinical practice. The data collected during unscheduled visits should be entered into the eCRF.

13 SAFETY PROCEDURES

13.1 Definitions

13.1.1 Safety Reporting Period

The safety reporting period is defined as the interval between the time of informed consent signature and the end of the designated follow-up period. The investigator must instruct the subject to report AEs and SAEs during this time period. Any medical and surgical event, or any laboratory findings considered as clinically significant by the investigator, that occurred between Screening Visit and Visit 1 (before the first dose has been administered) will be recorded as medical history.

13.1.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs include, but are not limited to the following: pre-existing conditions which worsen during the study, exacerbation of a pre-existing illness or increase in frequency or intensity of a pre-existing episodic event or condition. A condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study should also be reported as an AE. An AE occurring from abuse (example, use for non-clinical reasons) of a study product or an AE that has been associated with the discontinuation of the use of a study product should also be reported.

Determination of AE's should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked a non-specific question such as: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

13.1.3 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

- Death (Note: Death is an outcome, not an event)
- Life-threatening (Note: life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which could hypothetically have caused death had it been more severe)
- Inpatient hospitalization or prolongation of an existing hospitalization (Note: "inpatient hospitalization" refers to an unplanned, overnight hospitalization)

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly / birth defect
- Important medical event (as deemed by the investigator) that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above (e.g. intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions that do not result in hospitalization).

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, hospitalization or prolongation of hospitalization should not be reported as a SAE by the participating investigator. This is the case, in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g. stent removal after surgery). This should be recorded in the participant's study file.

Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, or meets any of the other SAE criteria, then the event is an SAE.

13.1.4 Clinical Laboratory Abnormalities and other Abnormal Assessments as AEs/SAEs

Abnormal laboratory findings and other abnormal assessments that are judged by the investigator as clinically significant must be recorded as AEs or SAEs if they meet the definition of an AE, as defined in section 13.1.2, or an SAE, as defined in section 13.1.3. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected after study drug administration or that are present at baseline and worsen following the start of the study are included as AEs or SAEs. The investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

13.1.5 Adverse Drug Reaction

An adverse drug reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

13.1.6 Unexpected Adverse Event or Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as

anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

13.1.7 Classification of Severity

All AEs must be rated on a 3-point scale of increasing severity using the following definitions:

MILD (Grade 1)	An adverse event that is easily tolerated by the subject causes minimal discomfort and does not interfere with everyday activities.
MODERATE (Grade 2)	An adverse event that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed
SEVERE (Grade 3)	An adverse event that prevents normal everyday activities; treatment or other intervention usually needed.

Further guidance concerning allocation of grading of individual events will be taken from the FDA guidance document "toxicity grading scale for adult and adolescent volunteers enrolled in preventive vaccine clinical trials". Please refer to: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

13.1.8 Classification of Relation to Investigational Medicinal Product

The investigator should make an assessment of whether the AE is likely to be related to the IMP according to the following definitions:

UNRELATED	A relationship to the study drug can be definitely ruled out (reasonable explanation must be given, e.g. involved in traffic accident while in back seat of car).
UNLIKELY	A relationship to the study drug is considered unlikely: the time relationship to the administration of study drug does not suggest a causal relationship and/or the underlying disease, other concomitant illnesses or medications appear more likely explanations according to present knowledge.
POSSIBLY RELATED	There is a reasonable possibility that the adverse event may have been caused by the study drug: there is a reasonable time relationship to the administration of study drug but the nature of the event, the underlying disease, and/or concomitant medication or concomitant illnesses suggest that other explanations are a significant possibility.
PROBABLY RELATED	The study drug is considered to be the most likely cause of the adverse event: there is a reasonable time relationship to the administration of the study drug and the event is considered unlikely to be not attributed to concurrent disease or concomitant medications.

13.2 Reporting of Adverse Events

If several signs, symptoms or diagnostic abnormalities are related to a medically defined diagnosis or syndrome, the diagnosis should be reported on the AE pages in the CRF. All related signs, symptoms and abnormal diagnostic procedures should be grouped together as a single diagnosis. Grouping into a medical diagnosis should only be done if every component sign and symptom is a medically and clearly acknowledged component of the diagnosis by standard textbook of medicine. If any aspect of the signs or symptoms does not fit into a classic pattern of the diagnosis or syndrome, a separate AE should be reported for each sign or symptom.

All AEs during the safety reporting period will be recorded on source documents. A diary will be given to the subjects/study partners/legal representatives to record any adverse event.

All AEs will be recorded in the CRF. For each sign, symptom or diagnosis, the Investigator will provide the following information: type of event, date initiated/observed, severity, action taken, seriousness, date stopped, outcome and relation to investigational medicinal product.

SAEs must be reported on a SAE report form and on the AE pages in the CRF.

Any SAE must be reported immediately by the investigator, within one calendar day (24 hours) from time of awareness by email to the Safety Officer below, who in turn will notify the Sponsor. This reporting routine will be described in a written procedure prior to start of screening.

SAE reporting:

All safety related information will be collected and processed promptly, to comply with regulatory requirements.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be notified to the Competent Authority and IRB/IEC in an expedited manner as follows: fatal or life-threatening SUSARs – as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information; non-fatal and non-life-threatening SUSARs - as soon as possible but no later than 15 calendar days after the sponsor determines that the information qualifies for reporting. Relevant follow-up information for fatal or life-threatening SUSARs will be provided to the FDA and IRB/IEC within an additional 8 calendar days.

Annual Safety Reports will be submitted to the Competent Authority by the Sponsor or legal representative and to IRB/IEC by the coordinating center.

13.3 Follow-up on Adverse Events

Any follow-up data will be detailed in a subsequent SAE form, which also must be reported to the Safety Officer, who will follow-up with the Investigator if additional information is needed.

Follow-up:

a) The investigator should take all appropriate measures to ensure the safety of the subjects, notably he should follow up the outcome of any SAEs (clinical signs, laboratory values or other, etc.) until the return to normal or until consolidation of the subject's condition.
b) All AEs must be followed until they are resolved or the subject's participation in the trial ends, i.e. until a final report is completed for that subject. Instructions for reporting changes in an ongoing AE during a subject's participation in the trial are provided in the instructions which accompany the AE Case Report Forms.
c) All *SAE*s and those *non-serious* events assessed by the Investigator as possibly related to the investigational study drug should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable". Resolution of such events is to be documented on the appropriate CRF.
d) Any serious adverse event brought to the attention of the investigator at any time after cessation of investigational study drug and considered by him/her caused by the trial treatment with a reasonable possibility should be reported to ProductLife.
e) For blinded trials, the code must be broken only in exceptional circumstances when knowledge of the investigational study drug assignment is essential for treating the subject.

13.4 Expected Signs and Symptoms

ACI-24 is a small peptide (anchored on liposomes) having not shown any systemic adverse reactions in animals.

Allergic reactions might, however, occur and a risk of anaphylactic reaction cannot be excluded. Minor local reactions at the injection site have been observed in some animals and may occur. Vital signs (blood pressure, heart rate and temperature) will be monitored during and for at least 4 hours after injections for any anaphylactic or allergic reactions.

Meningoencephalitis was observed in 6% of subjects with a previous vaccine against Aβ from Elan (AN1792); the current agent has been modified to reduce the risk of such reactions.

Studies with other agents have shown that amyloid modifying treatments may be associated with a range of imaging abnormalities (Sperling *et al.*, 2012), probably related to increased vascular permeability, which have been collectively termed ARIA (Amyloid Related Imaging Abnormalities) (Sperling *et al.*, 2011). These have been sub-classified into ARIA-E and ARIA-H as follows:

- ARIA-E includes FLAIR signal abnormalities on MRI thought to represent parenchymal vasogenic edema and sulcal effusions.

- ARIA-H includes abnormalities detectable on T2*-weighted gradient echo sequences that are thought to represent microhemorrhages and hemosiderosis. It should be noted that microhemorrhages are a frequent phenomenon in the spontaneous course of Alzheimer's Disease.

While most cases of ARIA are asymptomatic, in some cases edema may be associated with headache, confusion, visual, gait and other neurological disturbances. Newly developing ARIA, including asymptomatic microhemorrhages, requires suspension of dosing and monitoring with additional MRI scans at frequent intervals to ensure stabilisation. High dose steroids (e.g. iv dexamethasone) may be administered in the treatment of edema as clinically indicated.

13.5 Pregnancy

Pregnant women, women who plan to become pregnant, or women currently nursing an infant may not take part in this study. Women of childbearing potential will be asked to have a pregnancy test at screening, and again at Visit 1/Day 0/Baseline and at Visits 3, 5, 7, 10, 13 and 16 to exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive during the course of this study. An effective contraceptive is a method of birth control which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, transdermal patches, combined oral contraceptives, some intrauterine devices (IUDs), hormonal vaginal devices, sexual abstinence or vasectomized partner. Any woman who finds that she has become pregnant while taking part in the study including the SAE follow-up period should immediately contact the Investigator who should notify the coordinating center and Sponsor without delay. Women who become pregnant during the study will be withdrawn from the study and no further immunizations given. While not a SAE, pregnancy must be reported as an SAE. Pregnancy should be followed up until delivery.

For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.

13.6 Treatment of Adverse Events

Treatment of any AE is at the sole discretion of the investigator and according to current available best treatment. The applied measures should be recorded in the CRF of the subject. It is the responsibility of the Investigator to ensure the availability of facilities sufficient to handle emergency situations during the trial.

In the event of meningoencephalitis thought to be treatment related, consideration should be given to the use of steroids, since such treatment was reported in the AN1792 study to be associated with improvement in many cases (Orgogozo *et al.*, 2003).

13.7 Emergency Decoding

Decoding is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper handling of the subject. If the treatment code envelopes are broken, the reason and the date should be recorded and signed by the Investigator (see also 10.4).

13.8 Stopping Rules

13.8.1 Stopping at the Individual Patient Level

Dosing will be suspended at the individual level and in the study as a whole if clinically relevant meningoencephalitis considered possibly related to study drug is observed. Dosing will be halted at the individual level if vasogenic edema, macrohemorrhage, or an area of superficial siderosis or clinically significant microhemorrhages are observed by MRI and follow-up scans performed at least monthly to determine that it has stabilized or resolved. In symptomatic cases of vasogenic edema, intravenous corticosteroids (e.g. dexamethasone or methylprednisolone) should be administered as clinically indicated. Dosing will also be stopped at the individual level if a serious adverse event considered possibly or probably related to study drug occurs. Dosing will also be suspended at the individual level in the case of adverse reactions of moderate intensity (Grade II) persisting for more than 2 weeks or of severe intensity (Grade III) until further evaluation by the DSMB.

13.8.2 Stopping or Suspension of Dosing at the Study Level

Dosing will be suspended at the study level if clinically relevant meningoencephalitis is observed in any subject.

All serious adverse events will be reported to the DSMB who will evaluate them and recommend whether dosing in the study as a whole can continue. If two or more clinically relevant non-serious adverse reactions of moderate (Grade II) intensity persisting for more than 2 weeks or of severe intensity (grade III) are observed, the DSMB will evaluate the cases and determine whether dosing can continue in the study as a whole.

14 STATISTICAL METHODS AND ANALYSES

The presentation and analysis of data will be detailed in a Statistical Analysis Plan that will be approved by AC Immune.

14.1 General Information

Continuous data (e.g. age) will be presented with number of observations, mean value, standard deviation, median and range (minimum and maximum value). No hypothesis testing will be performed. Any statistical tests done will be considered as fully descriptive.

Categorical data (e.g. gender, family history, ethnicity) will be presented with number of observations within each category and percentage of subjects.

Missing values will not be replaced. However, a retrieved drop-out approach will be used meaning that subjects that withdraw from the trial will be asked to attend an end-of-trial visit, at which all scheduled assessments will be conducted where possible.

For AEs, any missing severity will be replaced with 'severe' and any missing information about whether the AE is stopped will be replaced with 'ongoing'. Any AE with missing relationship will be considered as possibly related to the study drug.

14.2 Sample Size

The sample size has been chosen as 6+2 per cohort. It is expected that the sample size will be sufficient to achieve the main goals of detecting common adverse events and providing information concerning immunogenicity of ACI-24 in this population.

If there is no safety concern for any of the cohorts, then the subjects receiving placebo (2 per cohort or, if applicable, 4 in case of expansion of one of the study cohorts) will be grouped into one group (4 subjects in total or 6 subjects in case of expansion of one of the study cohort) used for comparison of efficacy data between the two levels of active treatment and placebo. This is done under the assumption of no cohort effect such as seasonal differences, and differences in cohorts with respect to severity of the disease.

14.3 Analysis Sets

The modified intention-to-treat (mITT) analysis set is defined as all randomized subjects who receive at least one dose of the drug, i.e. of either ACI-24 300 µg antigen, ACI-24 1,000 µg antigen or placebo and who have at least one biological or efficacy assessment at any time during the study after the first dose administration.

Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The mITT analysis set will be used for presentation of efficacy, biological and brain imaging effects primary and secondary endpoints.

Since all visits include mandatory safety assessments, in practice the safety analysis set, used for analysis of safety data, is identical to the mITT analysis set.

The safety analysis set will consist of all randomized patients who received at least one dose of study drug, of either ACI-24 300 µg antigen, ACI-24 1,000 µg antigen or placebo and who have at least one post dosing safety assessment.

The safety analysis set will be used for summaries of safety.

The Per protocol analysis set (PP) is defined as all subjects included into the mITT dataset for whom no major protocol deviations were observed and who have completed Visit 18 and have had all injections per the protocol. The decision whether a protocol deviation is relevant or not for the exclusion of patients from the PP set will be made in a blinded data review meeting.

14.4 Primary Endpoints

14.4.1 Primary Safety and Tolerability Endpoints

14.4.1.1 Adverse Events

AEs occurring between first dosing and end-of-trial will be presented.

Overview of AEs will be given in terms of number and percentage of subjects per dose group experiencing:

- AEs
- SAEs
- Adverse drug reactions
- AEs leading to withdrawal
- Deaths

Moreover AEs will be coded according to MedDRA (actual version used will be specified in the clinical study report) and summarized by System Organ Class and Preferred Term.

AEs will also be summarized according to severity (mild, moderate, severe) and according to relationship to drug.

SAEs will be summarized by System Organ Class and Preferred Term. SAEs will also be summarized according to severity and relationship to drug.

14.4.1.2 Other Safety Endpoints

Other safety endpoints consist of:

1) Global assessment of tolerability
2) Physical examination
3) Neurological examination
4) Vital signs
5) Suicidal ideation/behavior
6) MRI Imaging
7) Electrocardiogram
8) Routine hematology and biochemistry evaluation in blood
9) Routine biochemistry evaluation in urine
10) Inflammatory markers in blood and CSF

Data will be summarized per measurement time and dose group. Change from baseline will be presented per dose group where available.

14.4.2 Primary Biological Endpoint

The primary biological endpoint consists of anti-Aβ1-42 Ig in serum.

The baseline value, in the case of antibody titer will be taken as the mean of the anti-$A\beta_{1-42}$ Ig titer values at Screening Visit [week -4 to 0] and Visit 1 [week 0].

Data will be summarized per measurement time and dose group. Change from baseline will be summarized per dose group where available.

No statistical testing will be done.

14.5 Secondary Endpoints

14.5.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints consist of:

- Clinical Assessments: Change from baseline as measured by Clinical Global Impression of Change
- Cognitive Assessments: Change from baseline in CANTAB motor control, reaction time, paired associative learning; Brief Praxis Test; behavior (change from baseline in Vineland Adaptive behavior scale; Neuropsychiatric Inventory)

Data will be summarized per measurement time and dose group. Change from baseline will be summarized per dose group where available.

The change over time in scores will be presented in a <score> vs. <time> plot, each dose group presented with different patterns.

No statistical tests will be performed on secondary efficacy endpoints because the sample size does not allow to make meaningful statistical inference.

14.5.2 Secondary Biological Endpoints

The secondary biological endpoints consist of:

- Whole brain, ventricle and hippocampal volume assessed by MRI
- T cell activation
- Biomarkers
- Anti-Aβ1-42 Ig in CSF

Data will be summarized per measurement time and dose group. Change from baseline will be summarized per dose group where available.

Raw data will be presented graphically in a line plot, presenting mean values per dose group versus time.

A graphical display of percent change from baseline at each measurement time per dose group will be prepared.

The secondary biological endpoints (e.g. Whole Brain Volume) will be assessed descriptively.

If the number of CSF samples is sufficient, anti-Aβ Ig titer (Aβ1-42) will be analyzed from CSF collected at Visit 1 [week 0] and Visit 17 [week 50]. Change from baseline [week 0] at Visit 17 [week 50] will be summarized per dose group. No statistical testing will be done.

15 DATA HANDLING

15.1 Data Handling

Study data collected by the investigator or staff authorized by the investigator will be collected using a web-based electronic data capture (EDC) system. Each subject will be assigned a unique subject number at screening and will keep this number for the duration of the study even if he or she transfers to another site. Subject numbers will not be reassigned or reused for any reason. Subjects who discontinue or withdraw from the study before receiving a treatment assignment code, but who reenroll at a later time must be reassigned a new subject number. Subjects should be identified to the sponsor only by their assigned subject number, date of birth, and sex.

15.2 Electronic CRFs

Following training, trial staff will be given access to the EDC system. Access to the EDC system is restricted to trial staff participating in the trial and the extent of access will depend on the participants' user role in the trial. eCRF Completion Guidelines will be provided to the sites.

Data recorded in the eCRFs will be accessible to trial staff through a secure internet connection.

The investigator or staff authorized by the investigator should enter subject data into electronic eCRFs in a timely manner. A separate eCRF will be used for each subject enrolled. The eCRFs must be maintained in an up-to-date condition at all times by the investigator or designee. The completed eCRFs will be signed by the investigator, or co-investigator(s) authorized by the investigator. This signature information (including date of signature) will be kept in the audit trail and is unalterable. Only medically qualified (co)investigators can sign data on clinical assessments/safety.

Any correction(s) made by the investigator, or authorized site staff, to the eCRF after original entry will be documented in the audit trail. Changes to data already approved, requires the re-signature of investigator or authorized staff. The audit trail will identify the person making the change and the date, time and reason for the change.

After data entry, systematic data validation will be performed and any data discrepancies will be presented electronically to the site staff through the EDC system.

Queries for discrepant data may be generated automatically by the software upon entry or generated manually by the monitor or the trial data manager(s). All queries, whether generated by the system or by trial staff, will be in electronic format.

The trial monitor will check the eCRFs for accuracy and completion and perform source data verification (SDV). The trial monitor will document electronically SDV of all sections of eCRFs used.

The systematic data validation will provide a clean and consistent database prior to the statistical analysis. Data will be processed in accordance with the general terms and conditions of any national legislation.

The eCRFs will be available for inspection by authorized representatives from sponsor, e.g. co-monitoring or audit by the Sponsor, from Regulatory Authorities and/or EC.

15.3 Record Retention

For archiving purposes, each investigator will be supplied with a copy of the eCRFs, for all subjects enrolled at the site, via an electronic medium at completion of the trial. Audit trail information will be included.

The investigational sites will maintain all trial documentation, and take measure to prevent accidental or premature destruction of these documents.

To enable evaluations and/or audits from Health Authorities or sponsor, the investigator agrees to keep records of all study documentation, including between others the identity of all participating subjects, all original signed Informed Consent Forms, a copy of all eCRFs, and detailed records of drug disposition. These should be kept in an Investigator's File that should be provided by the Sponsor and kept regularly updated by the Investigator.

To comply with international regulations, the records should be retained by the Investigator for 15 years or longer in accordance with national regulations after the end or termination of the trial, or 2 years after the marketing authorization or the sponsor has discontinued its research with respect to such drug. The investigational sites must notify the sponsor in writing before destroying any data or records.

15.4 Source Data Verification and Quality Control

Source Data Verification (SDV) is a key function in assuring the Sponsor that clinical trial information is recorded and handled in a way that allows its accurate reporting, interpretation and verification. Monitors will perform SDV during the conduct of the trial, to confirm the accuracy and completeness of eCRFs, and consistency of source documents and other trial related records against each other. To enable SDV at the trial site, it is essential to establish and agree with the investigator what constitutes source data/documents for the trial data to be collected. The location of source data will be defined in the Location of Source Data Form prior to initiation of the trial.

All trial data reported in the eCRFs should be verifiable from source documents, unless agreed differently with the Sponsor.

Global Assessment of Tolerability and Clinical Global Impression of Change Scale (CGIC) score can be recorded directly in the eCRF, and the eCRF will in this case be considered the source document for these data.

The subjects/study partners/legal representatives will be given the opportunity to record any adverse event in a diary. The diaries will not be considered as source data.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

16 MONITORING

Regular monitoring visits by representatives of the sponsor will be made during the study.

Monitoring will begin with an initiation visit prior to study commencement to clarify all aspects of the protocol and documentation. The purpose of later visits during the implementation period will be to evaluate study progress and adherence to the protocol. The visit intervals and detailed monitoring activities will be defined in Monitoring Guidelines. The monitoring activities will be performed by blinded monitors, except for monitoring product accountability which will be done by unblinded monitors specifically assigned for the duration of the study. Unblinded monitors will ensure that the subjects' treatment assignment (active drug or placebo) is kept confidential during the entire duration of the study.

During these monitoring visits the monitor must have full access to data and documents as she/he will check case report forms for completeness, clarity and consistency with the information in subject files (source data checking). In all cases, it is the responsibility of the monitor to maintain subject confidentiality.

A report will be written by the unblinded and blinded monitor after each visit. Each report from the blinded monitor will be distributed to the coordinating center for review and approval. The reports from the unblinded monitor will be kept separately at the coordinating center, not accessible to any blinded staff.

Blinded monitoring reports will be stored in the TMF throughout the study. Unblinded monitoring reports will be sent to the Sponsor at the end of the study and will then be stored in the TMF.

17 RESPONSIBILITIES

17.1 Responsibilities of the Investigator

The investigators are responsible for the following:

- Obtain the written and dated approval of the local IRB/IEC prior to beginning the study (national regulatory approvals will be obtained from the Sponsor)
- Selection of participants in accordance with the inclusion and exclusion criteria; obtaining the informed consent of the subject and study partner/legal representative
- Maintain a Subject Identification Log linking the subject number to the subject's name. The investigator must maintain confidentiality of subjects and potential subjects in accordance with the Declaration of Helsinki. Information that could identify a subject will be masked on material received by the sponsor
- Maintain a list of qualified persons to whom she/he has delegated specific study related activities
- Adherence to the study protocol and the spirit of good clinical practice. If modification of protocol becomes necessary, the rationale will be provided in a signed protocol amendment for submission to the IRB/IEC (national regulatory approvals will be obtained from the Sponsor)
- Accurate and complete data collection
- Identification of AEs with notification to sponsor and IRB/IEC, as applicable
- Co-operation with monitoring visits and external audits
- Complete and maintain the Investigator Site File up-to date
- Archiving of the Investigator's File (including the original signed informed consent forms of all subjects) for at least 15 years or longer in accordance with national regulations after the end or termination of the trial, or 2 years after the marketing authorization or the sponsor has discontinued its research with respect to such drug.

17.2 Responsibilities of the Sponsor

The sponsor is responsible for the following:

- Obtaining the written and dated approval of the national regulatory authorities prior to beginning the study
- Preparation of study products under Good Manufacturing Practice
- Product labeling to maintain blinding per protocol
- Delivery of study products to study site with shipment records
- Distribution of study related documents and sample collection supplies (as needed) to clinical site
- Adherence to the study protocol. If modification becomes necessary, the rationale will be provided in a signed protocol amendment.
- Regular study monitoring
- Obtaining insurance protection
- Retaining the study records (including the original case report forms) for 15 years after the end or termination of the trial.

18 PROTOCOL COMPLIANCE

The clinical site should conduct the study in compliance with the protocol and should not implement any deviation from, or changes of the protocol.

Protocol deviations should be avoided.

If deviations occur at site, the clinical site should inform the Monitor. Protocol deviations will be documented, stating the reason, date, action(s) taken, and the impact for the subject(s) or study. The documentation will also specify if any corrective action apply.

Study drug errors should be reported as protocol deviations. Study drug errors are the result of administration or consumption of the wrong product, and/or administration or consumption by the wrong subject, and/or administration or consumption at the wrong time and /or by the wrong administration route, due to human error.

Study drug errors include, but are not limited to the following;

- Over dose of study product whether accidental or intentional (Overdose is a dose greater than that specified in the protocol)
- The administration of a study product that has not been assigned to the subject.
- Administration of expired study product when it is associated with an AE.
- Errors involving rate of administration, reconstitution and dilution, including use of appropriate diluent and the timeframe in which study product should be used after reconstitution and /or dilution.
- Errors related to storage refrigeration requirements

The investigator may however implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favorable opinion. The implemented deviation or change will be submitted as soon as possible to the Sponsor and appropriate action will be undertaken to inform the IRB/IEC and regulatory authorities.

The documentation will be filed in the Investigator Site File and in the Trial Master File.

The investigator must not make any changes to the study without IRB/IEC and sponsor approval except when necessary to eliminate apparent immediate hazards to subjects may be implemented immediately, but any significant change must then be documented in an amendment that will be submitted to the Competent Authority and IRB/IEC. All protocol amendments must be reviewed and approved following the same process as original protocol.

19 LEGAL REQUIREMENTS

The trial will be conducted in the United States in adherence with the relevant legal requirements of the country. The study will be submitted to FDA and IRB/IEC in accordance with national regulations.

19.1 Ethical Aspects

19.1.1 Protection of Subject's Confidentiality

Confidentiality of all study participants will be maintained; codes for subject identification will be utilized and the data files will be encrypted.

19.1.2 Informed Consent

The written informed consent procedure should comply with any applicable regulatory requirement(s) and should adhere to GCP/ICH guidelines and to the ethical principles that have origin in the declaration of Helsinki, as defined below but not limited to:

[Local country regulatory requirements regarding written informed consent procedure should prevail]

- The written informed consent must be obtained before any study specific procedures have been undertaken.
  - The investigator (or a study site staff designated by the investigator as per local country regulations), must obtain a written informed consent signed and personally dated by the subject.
  - As subjects with Down syndrome may not be able to make an independent decision about their participation in the study, the subjects' study partner/legal representative (as defined per local country regulatory requirements) must also sign the informed consent form to ensure that the subject participates in the study voluntarily and has been informed adequately.
- The written informed consent form must be completed in two copies: one original should be kept in the Investigator's file and one provided to the subject/study partner/legal representative.

At time of informed consent discussion, subjects will be proposed to be part of a study subgroup, to allow that lumbar puncture is done at Visit 1 [week 0] and Visit 17 [week 50] in order to collect CSF. If a subject agrees on lumbar puncture, the subject and the study partner/legal representative will be requested to sign a separate informed consent. If a subject or the study partner/legal representative disagrees that lumbar puncture is done, the subject will be allowed to participate to study, with the condition that no CSF samples are collected.

Subjects and subjects' authorized representative may withdraw consent throughout the study, whenever they consider appropriate to do so. If a subject or the study partner/legal representative

withdraws his/her informed consent on lumbar puncture, the subject can continue to participate to the study, with the condition that no further CSF samples are collected.

19.1.3 Ethics Committee

The study protocol and mandatory study documents will be submitted by the Investigator for examination to IRB/IEC. Commencement of the clinical trial is not permitted without written approval of the IRB/IEC and competent authorities.

The IRB/IEC must be notified of all subsequent additions or changes in the study protocol. Notification of the IRB/IEC is also required in the event of SAEs during the clinical trial. Annually summaries of the trial status, Clinical Trial Reports or other documents will be submitted as required by the IRB/IEC.

19.2 Regulatory Authorities

Regulatory authorities will receive the Investigational New Drug (IND) Application, substantial/non-substantial amendments to the protocol, reports on SAEs, and Clinical Trial Reports according to national requirements.

Commencement of the clinical trial is not permitted without written approval of the IRB/IEC and competent authorities.

19.3 Declaration of Helsinki

The trial will be conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments.

20 QUALITY ASSURANCE

20.1 Good Clinical Practice (GCP)

This clinical trial will be conducted following the principles of ICH (International Conference on Harmonization) guideline for Good Clinical Practice and ethical principles that have their origins in the declaration of Helsinki and adherence with the applicable regulatory or legal requirements.

20.2 Internal Quality Control

Psychometric data will be reviewed regularly during the study for plausibility and consistency and appropriate discussion with the study site held where any concerns arise from this review. Imaging interpretation will be made by a board certified neuroradiologists.

21 REPORTS AND PUBLICATIONS

Safety Reports will be submitted as described in Section 13, Safety Procedures.

Progress reports will be submitted to the IRB/IEC annually or more frequently, if requested by the IRB/IEC and to regulatory authorities.

IRB/IEC and competent authority will be informed about the study completion and they will be provided with the final study report.

The sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

Rights for publications are defined in contracts between participating sites and Sponsor.

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