Statistical Analysis Plan

Sponsor: AC Immune SA

Protocol number: ACI-24-1301 (2144/ACI)

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

Protocol Version: Version 5.0, 28 January 2020

IND Number: 15342

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Version	Date
Draft 0.1	10 October 2016
Draft 0.2	15 November 2016
Draft 0.3	19 December 2016
Draft 0.4	20 December 2016
Draft 0.5	17 November 2017
Draft 0.6	05 December 2017
Draft 0.7	14 May 2018
Final Draft 1.0 (unsigned but issued for programming/coding purposes)	14 May 2018
Draft 1.0a	17 December 2019
Draft 1.0b	27 April 2020
Draft 1.0c	09 June 2020
Draft 1.0d	25 August 2020
Draft 1.0e	15 September 2020
Final 2.0	18 September 2020

Approval

Upon review of this document, including table layouts, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

Signature	Date
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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
Aβ	β-amyloid
BLQ	Below limit of quantitation
BPT	Brief praxis test
CANTAB	Cambridge neuropsychological test automated battery
CGI	Clinical global impression
CGIC	Clinical global impression of change
(e)CRF	(electronic) case report form
C(N)S	Clinically (not) significant
CSF	Cerebrospinal fluid
CSR	Clinical study report
C-SSRS	Columbian suicide severity rating scale
CTCAE	Common terminology criteria for adverse events
DS	Down Syndrome
DSMB	Data safety monitoring board
e.g.	For example
i.e.	That is
ICF	Informed Consent Form
ICH	International conference on harmonization
(m)ITT	(modified) Intent-to-treat
KBIT-2	Kaufmann brief intelligence test - 2
LLOQ	Lower limit of quantitation
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
NCS	Not clinically significant
NPI	Neuropsychiatric inventory
PPS	Per-protocol analysis set
PT	Preferred term
RBANS	Repeatable battery for the assessment of neuropsychological status
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan

SD	Standard deviation
SEM	Standard error of the mean
SHCR	Contract research organization: SynteractHCR Deutschland GmbH, Albrechtstr.14, 80636 Munich, Germany
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings, figures
VABS-II	Vineland-II adaptive behavior scale II
WHO	World Health Organization
WHO-DDE	WHO drug dictionary enhanced

DEFINITIONS

Adverse Event (AE)	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. AE 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.
Adverse Drug Reaction (ADR)	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.
Serious AE (SAE)	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 subject 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) • Insubject hospitalization or prolongation of an existing hospitalization (Note: “Insubject

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 subjects 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. 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.

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.

Reporting time of adverse events	The safety reporting period is defined as the interval between the time of informed consent signatures and the end of the designated follow-up period. Any medical and surgical event that occurred between Screening Visit and Visit 1 (before the first dose has been administered) will be recorded as medical history. All AEs during the safety reporting period will be recorded on source documents. A diary will be given to the subjects/legal representatives to record any adverse event. All AEs will be recorded in the CRF.
Study vaccine	Throughout this SAP, the terms "IMP" or 'study drug' or 'drug' refer to the preferred term 'study vaccine' for the final clinical study report.
Absolute value	The unadjusted reported result of a certain variable
Change from baseline	The arithmetic change from baseline defined as: absolute value at post-baseline visit – absolute value at baseline
Percent change from baseline	The percent change from baseline defined as: (absolute value at post-baseline visit – absolute value at baseline) / absolute value at baseline * 100

1 INTRODUCTION

This document outlines the statistical methods to be implemented during the analysis of data collected within the scope of AC Immune SA ACI-24-1301 (2144/ACI) study. The purpose of this plan is to provide analyses strategies for all study data which were collected, as well as to provide specific guidance how to analyze data for the statistical analysis.

Any deviations from this plan will be documented in the clinical study report (CSR).

2 STUDY DOCUMENTS

The following study documents are used for the preparation of the SAP:

- Protocol version 5.0, 28JAN2020
- Annotated CRF 4.0, 12DEC2017
- Data Management Plan 3.0, 20SEP2019

3 STUDY OBJECTIVES

3.1 Primary objectives

Safety related:

- To assess the safety and tolerability of ACI-24 in adults with Down Syndrome

Biological related:

- To assess the effect of different doses ACI-24 on induction of anti-Aβ Ig titer in serum

3.2 Secondary objectives

Efficacy related:

- 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 using CANTAB, BPT and the clinical rating scale assessments VABS-II and NPI

Biological related:

- 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 (as applicable) 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. Note: Objective is taken from protocol, see also sec. 15.1 Changes to endpoints)
- To assess the effect of different doses ACI-24 on induction of anti-Aβ Ig titer in CSF* (*in subgroup)

4 STUDY DESIGN AND PLAN

The AC Immune SA ACI-24-1301 (2144/ACI) study is a prospective multi-center, placebo-controlled, double-blind and randomized (3:1) study of 2 doses of ACI-24 treatment versus placebo over 24 months. The subject population consists of subjects with Down Syndrome (DS) at the age of 25 – 45 years suitable for treatment of β-amyloid (Aβ) related cognitive decline. The study is conducted in the United States with approximately five study sites.

The study contains 2 dose-cohorts of 8 subjects each (6 subjects on ACI-24 300 µg, 6 subjects on ACI-24 1,000 µg, 2 subjects on placebo in each dose-cohort) with seven s.c. injection visits at month 0, 1, 2, 3, 6, 9 and 12 with 12 months treatment free safety follow-up. The dose-cohorts are studied sequentially in ascending dose order (dose-cohort 1: 300 µg antigen or placebo, dose-cohort 2: 1,000 µg antigen or placebo). The 2nd dose-cohort was expected to start once safety and tolerability data up to visit 8 (week 14) of the last subject of the preceding cohort have been reviewed by a Data Safety Monitoring Board (DSMB).
The number of participants in the optimal dose-cohort was planned optionally to 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 was 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 was planned to 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 was 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).

Within cohorts, there was 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 overall treatment phase lasts 12 months, all subjects are then followed up for 12 months after the last dose with a final safety and efficacy assessment.

Subjects were seen by the investigator at Screening Visit (week -4 to 0) and if eligible, randomized in the study.
The treatment period lasted 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 at week 66 and week 84. Within each cohort, the duration of a subject's participation is 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 was 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 were 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).

Study Plan		Treatment Period																		Follow-up Period				
Visit Number	Scree-ning	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	Ph. call	V20	Ph. 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 Inf. / Consent	•																							
MedHist, Conc. Illnesses, Demographic Data	•																							
InEx Criteria	•	•*																						
(incl. KBIT-2 at Vs only)	•																							
Withdrawal Criteria			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant Medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vital signs	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		•		•
Glob. Ass. of Tolerability			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•					
Phys., neurol. examination	•	•	•	•	•	•	•	•	•		•	•		•	•		•	•		•		•		•
CANTAB, RBANS[1] and BPT	•	•										•						•				•		•
Vineland and NPI		•										•						•				•		•
CGIC (≠ baseline interview)		•≠							•			•			•			•		•		•		•
Suicidal ideation / behavior	•	•																•						•
Lumb.punct.CSF (subgroup)		•																•						
MRI / PET[2]	•								•			•						•						•
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 of protocol)	•																							
Urine																								
- *Routine evaluation*	•	•	•		•		•		•			•			•			•		•		•		•
- *Pregnancy test*		•		•		•		•			•			•			•							

* Any results obtained during Screening will be reviewed at Visit 1 [week 0] to ensure that the subject still fulfills In- / Exclusion Criteria, [1] RBANS was removed as an assessment per amendment 3, [2]PET scan was removed as an assessment per amendment 2.
**TLR4 blood samplings have been collected on site as per the previous versions of the protocol (v1.0 to v4.0) however the related TLR4 laboratory testing will not be performed according to clinical study protocol v5.0.

Table 1: Study plan

5 DETERMINATION OF SAMPLE SIZE

The sample size has been chosen as 6 + 2 (active + placebo) per cohort. It is expected that the sample size is 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 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.

The number of subjects will therefore consist of 16, means two dose-cohorts of 8 subjects each (6 active, 2 placebo). In case of optional expansion, a total of 24 randomized subjects were planned by expanding the optimal dose cohort to additional 8 subjects.

6 GENERAL ANALYSIS CONSIDERATIONS

The presentation of statistical analyses results will use standard summary tables (including in general mean, standard deviation, median, minimum, maximum or counts/ percentages), listings, and figures (tables, listings and figures = TLFs). The International Conference on Harmonization (ICH) numbering convention will be used for all TLFs.

No inferential statistical testing procedures will be applied. Exploratory correlations may be done. These may include correlation of antibody titer and changes in other readouts (for e.g. biomarkers in plasma such as Aβ), as well as other correlations not described in this SAP. Other summaries (e.g. quartiles, 95% confidence intervals, SEM) may be used as appropriate and will be mentioned in the respective sections. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. Percentages for missing values will be omitted and will not account for the percent calculation of other non-missing categories. Percentages will be therefore routinely based on the total category count excluding the missing category if not otherwise mentioned. Percentages showing a rate relative to the total number of subjects in this group will be given in special tables (e.g. AE tables). Footnotes will specify the percent basis in those cases.

All summary tables will be presented by treatment group, whereas treatment groups are sometimes pooled (see sec. 7). Summaries will also include a total summary column. Individual subject data obtained from the electronic case report forms (eCRFs), results from external laboratories and any derived data will be presented by subject in data listings.

The SAP text will only reference relevant listings, otherwise refer to the table of contents for listings, see section 16.3.2.

Subjects' data concerning screening failures will be listed only.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® Version 9.4 or higher. Tables, listings, and figures will be presented in ASCII format. Upon completion, all SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the Biostatistics lead or designee.

7 NOTATION OF TREATMENT GROUPS AND VISITS

7.1 Notation of treatment groups

The following notation of **cohorts/treatment groups** will be used throughout the report:

Full notation (as used in the study protocol)	***Notation as used throughout all tables, listings and figures***
Dose-cohort 1 and dose-cohort 2 pooled	ACI-24 (pooled) *or*
Dose-cohort 1 (300 µg antigen):	ACI-24 300 µg
Dose-cohort 2 (1,000 µg antigen):	ACI-24 1,000 µg
Placebo pooled	Placebo (pooled) *or*
Placebo corresponding to dose-cohort 1	Placebo coh1
Placebo corresponding to dose-cohort 2	Placebo coh2

Note: The **placebo groups** corresponding to dose-cohort 1 and dose-cohort 2 will be **pooled** for some analysis: study population (sec. 10), efficacy (sec. 12) and biological endpoint (sec. 13) analyses will require the pooled placebo group (Placebo (pooled)).

Safety analyses (sec. 11) and other safety and supportive analyses (sec. 14) will need the two individual placebo groups. For safety analyses there will be one exception in display: Analyses of ApoE genotyping uses pooled verum cohorts and pooled placebo groups for display of analyses results.
Table presentation will use the notations as mentioned above accordingly.
Listings will generally show variables either by cohort (cohort 1, cohort 2) or by treatment group (ACI-24 300 µg, ACI-24 1,000 µg, Placebo).

Note that analyses in sec. 10 (study population), 12 (biological endpoints) and 13 (efficacy endpoints) will use planned treatment and analyses in sec. 11 (safety) and 14 (extent of exposure and study duration) will use the actual treatment.

Listings will use treatment groups correspondingly.

7.2 Responder subgroups within treatment groups

Within each treatment group responders will be determined using IgG by free MSD method. This will lead to the following groups:

Full notation	***Notation as used throughout all tables and figures***
Dose-cohort 1 and dose-cohort 2 pooled, IgG responder Dose-cohort 1 (300 µg antigen), IgG responder Dose-cohort 2 (1,000 µg antigen), IgG responder by IgG responder	ACI-24 (pooled) responder *or* ACI-24 300 µg responder ACI-24 1,000 µg responder
Dose-cohort 1 and dose-cohort 2 pooled, IgG non-responder Dose-cohort 1 (300 µg antigen), IgG non-responder Dose-cohort 2 (1,000 µg antigen), IgG non-responder by IgG responder	ACI-24 (pooled) non-responder *or* ACI-24 300 µg non-responder ACI-24 1,000 µg non- responder
Placebo pooled	Placebo (pooled)

7.3 Visit terminology

Visit	*Notation as used throughout all tables, listings and figures***	*Alter-natively***	*Study part*
Screening Visit: Days -28 to Visit 1	Screening		Screening
Visit 1*: Week 0 (+3 days)	Visit 1 (week 0)	V1	Treatment period
Visit 2: Week 2 (±3 days)	Visit 2 (week 2)	V2	
Visit 3*: Week 4 (±3 days)	Visit 3 (week 4)	V3	
Visit 4: Week 6 (±3 days)	Visit 4 (week 6)	V4	
Visit 5*: Week 8 (±3 days)	Visit 5 (week 8)	V5	
Visit 6: Week 10 (±3 days)	Visit 6 (week 10)	V6	
Visit 7*: Week 12 (±3 days)	Visit 7 (week 12)	V7	
Visit 8: Week 14 (±3 days)	Visit 8 (week 14)	V8	
Visit 9: Week 16 (±3 days)	Visit 9 (week 16)	V9	
Visit 10*: Week 24 (±3 days)	Visit 10 (week 24)	V10	
Visit 11: Week 26 (±3 days)	Visit 11 (week 26)	V11	
Visit 12: Week 28 (±3 days)	Visit 12 (week 28)	V12	
Visit 13*: Week 36 (±3 days)	Visit 13 (week 36)	V13	
Visit 14: Week 38 (±3 days)	Visit 14 (week 38)	V14	
Visit 15: Week 40 (±3 days)	Visit 15 (week 40)	V15	
Visit 16*: Week 48 (±3 days)	Visit 16 (week 48)	V16	
Visit 17: Week 50 (±3 days)	Visit 17 (week 50)	V17	
Visit 18: Week 52 (±3 days)	Visit 18 (week 52)	V18	
Visit 19: Week 60 (±10 days)	Visit 19 (week 60)	V19	Follow-up
Phone call 1: Week 66 (±10 days)	Phone Call 1 (week 66)		
Visit 20: Week 72 (±10 days)	Visit 20 (week 72)	V20	
Phone call 2: Week 84 (±10 days)	Phone Call 2 (week 84)		
Visit 21: Week 96 (±10 days)	Visit 21 (week 96)	V21	End of Study (EoS)
Phone call between Visit 20 and Visit 21: For subjects due to delayed final visit (COVID-19 pandemic)	Unscheduled visit x	Unsched x	

*: Treatment application – immunizations
**Figure visit notation will be abbreviated where needed (V1-V21) in case space is limited. For (individual subject) profiles displaying time-series, the x-axis will show weeks 0, 2, 4, etc. instead of V1, V2, V3 etc.

COVID-19 pandemic issue:
Due to the COVID-19 pandemic the end of study visit at week 96 will be delayed for some subjects and an intermittent additional phone call will be introduced to collect safety data.

8 ANALYSIS POPULATIONS OR ANALYSIS SETS

The following subject populations will be used for the analyses as specified afterwards:

1. **All subjects analysis set (ALL):** All subjects who were screened in the study will be included in the ALL subjects set.
2. **Safety Analysis Set (SAF):** All randomized subjects who have 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 had at least one post dosing safety assessment will be included in the SAF subjects set.
3. **Modified intent-to-treat population (mITT):** All randomized subjects who have received 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 had at least one biological or efficacy assessment at any time during the study after the first dose administration. Following the intent-to-treat principle, subjects will be analyzed according to the treatment they were assigned to at randomization.
4. **Per-Protocol Analysis Set (PPS):** The per-protocol-set is defined as all subjects included into the mITT dataset for whom no major protocol deviation criteria, which are expected to affect interpretation of safety or efficacy, were observed, who have completed Visit 18 and have had all injections per the protocol.

Protocol deviations will be determined in a blind data review meeting (BDRM) before hard lock of the data base according to SynteractHCR's SOPs.

The respective analyses will be conducted using the following analysis sets:

- ALL: presentation of information on subject disposition, withdrawals and protocol deviations
- SAF: This population will be used for summaries of safety.
- mITT: This population will be used for summaries of (primary and secondary) efficacy and biological effects.
- PPS: This population will be used for additional summaries of efficacy and biological effects.

Study population data in sec. 10. will be prepared for all analysis sets.

9 HANDLING OF DROPOUTS OR MISSING DATA

9.1 General data handling of missing values

In general no imputations will be made for missing values. Summaries will be based on observed data/ valid cases only.

However, in exploratory analyses, a retrieved drop-out approach could be used meaning that subjects that withdraw from the study will be asked to attend an end-of-study 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.

For previous and concomitant medication, the following rules will be applied to impute missing start/ end dates (the calculation of durations if foreseen will not use imputed data):

Date	***Imputation rule***
Partial/ Missing Start Date	• Missing day - Impute the 1st of the month unless year and month is same as year and month of first dose of study drug then impute first dose date • Missing day and month – impute 1stJanuary unless year is the same as first dose date then impute first dose date • Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date
Partial/ Missing End Date	• Missing day - Impute the last day of the month unless year and month is same as year and month of last dose of study drug then impute last dose date • Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date • Completely missing – impute date of last dose • If imputed end date < imputed start date, take the imputed start date to impute the end date

9.2 Data handling during COVID-19 pandemic

The regular end of study visit 21 at week 96 cannot be performed in time for some subjects due to the COVID-19 pandemic situation, but will be delayed or subjects are withdrawing their consent and will not perform their final study visit. To ensure safety of subjects a phone call will be done between visits 20 and 21. During this phone call data

on selected variables (e.g. visit date = date of phone call, adverse events, reason for unscheduled visit, general comments, exit form in case subject wants to quit) will be collected. Others will remain as non-conducted investigations with a corresponding comment given as reason (‘phone call done due to COVID-19‘). These are eCRF sections vital signs, physical examination, MRI, ECG, central laboratory and local laboratory (ESR). Weight will remain missing at this phone call.

Results from such phone call visits will be listed only.
For subjects who withdraw the study earlier due to COVID-19, the study exit form will denote this and entries will be summarized accordingly.

The missing data from such subjects will not be imputed. Summaries will be based on observed data/ valid cases only. See also section 9.1.

10 STUDY POPULATION

10.1 Subject numbers per site

For each site, subject numbers by treatment group and overall will be displayed with counts and percentages.

10.2 Subject disposition and screening failures

Subject disposition information will be summarized for all subjects by treatment group and overall. Summaries will include number of screening failures, number of screened subjects, number of re-screened subjects, number of randomized subjects, number of subjects in each analysis set, as well as the number of subjects completing the study.

10.3 Study closure form/Exit form

Discontinued subjects, reasons for their discontinuations and blind code breakings will be summarized: The number of subjects who discontinued the study will be tabulated by treatment group with counts and percentages. In addition, for subjects who discontinued, the primary reason and whether there has been an associated blind code breaking will be tabulated by treatment group.

10.4 Protocol deviations

Classification of protocol deviations will be undertaken during a data review meeting. Subjects having protocol deviations and the specification of their protocol deviations will be listed only. Protocol deviations related to COVID-19 will be explicitly mentioned as such in a further category.

10.5 Demographic and baseline characteristics

10.5.1 Informed consent for study participation and for CSF sampling

Data on informed consent for study participation and for CSF sampling will be listed only.

10.5.2 Demographics

A summary table for the demographic data will be prepared with summary statistics for age at signing the ICF (years), age in each age group (by using the median age of subjects in cohorts 1, 2, and placebo, subjects will be split into two groups), gender, race, ethnicity

and years of education by treatment group. BMI (kg/m²) and K-BIT2 results (IQ composite) with corresponding lower and higher 90% confidence intervals at screening (unstratified and stratified by median split KBIT-2 IQ composite, see sec. 10.5.4. for derivation) will be included in the table.

10.5.3 Child bearing potential

Data on child-bearing potential will be listed only.

10.5.4 Kaufmann brief intelligence test (KBIT-2)

K-BIT2 results (IQ composite) with corresponding lower and higher 90% confidence intervals will be tabulated in the demographics table (see sec. 10.5.2). K-BIT2 results will be used to categorize subjects into two groups using the median K-BIT2 IQ composite value of all subjects of cohorts 1, 2 and placebo. For each of the subgroups descriptive measures of the IQ composite will be presented as well.

10.5.5 Medical history and concomitant illnesses

Medical history will be coded along the MedDRA 19.1 coding system or higher. Tabulation will use system organ class (SOC) and preferred term (PT) classification. The analysis will include summary tables displaying counts and percentages of subjects having a documented medical history by SOC and PT. If a subject has more than one medical indication which codes to the same PT, the subject will be counted only once for that PT. The total number of medical indications documented per SOC and PT will also be displayed. Details concerning diagnosis verbatim, start and end date of medical history, etc. will be displayed in a listing.

10.5.6 In- and exclusion criteria and eligibility

Data on in- and exclusion criteria and eligibility data will be listed only.

10.5.7 Other baseline characteristics at screening

Analyses of other screening variables not mentioned in the above sections, which are evaluated at Screening Visit and have further evaluations after the Screening Visit will be described in the following sections:

- Vital signs: see sec. 11.4.7
- Cambridge neuropsychological test automated battery (CANTAB): see sec. 13.8.2

- Repeatable battery for the assessment of neuropsychological status (RBANS): see sec. 13.8.3 – mentioned for completeness reasons: RBANS was removed in protocol v4.0 (amendment 3). Data entered in the eCRF up to this time point will be listed.
- Brief praxis test (BPT): see sec. 13.8.4
- Suicidal ideation/ behavior: see sec. 11.4.10
- Columbia suicide severity rating scale (C-SSRS): see sec. 11.4.11
- Magnetic resonance imaging (MRI)/PET: see sec. 12.4.4. Ad PET: only mentioned at this place for completeness reasons, but PET was not further requested due to protocol v3.0 (amendment 2). PET data entered in the eCRF will be listed.
- Electrocardiogram (ECG): see sec. 11.4.12
- Central laboratory: Hematology, biochemistry (including CRP), safety urine analysis, urine pregnancy test, see sec. 11.4.13.2- 11.4.13.7
- Central laboratory: Anti-Aβ Ig, see sec. 12.4
- Local laboratory: ESR, see sec. 11.4.13
- Physical and neurological examination, see sec. 11.4.5 and 11.4.6

11 SAFETY AND TOLERABILITY ANALYSES

11.1 Safety endpoints

Safety endpoints are assessed as follows:

1. Adverse events (Type and frequency)
2. Global assessment of tolerability
3. Physical and neurological examination
4. Vital signs
5. Suicidal ideation/ behavior
6. MRI
7. Electrocardiogram (ECG)
8. Routine hematology/biochemistry in blood
9. Routine hematology/biochemistry in urine
10. Inflammatory markers in blood
11. Inflammatory markers in CSF (if applicable)

11.2 Baseline values

Baseline values are the ones measured shortly before the administration of the immunization treatment. This is in most cases the Visit 1 (week 0), except MRI and ECG, which have no measurements at Visit 1 but at Screening Visit.

11.3 Calculation of change from baseline, percent change from baseline

If change from baseline or percent change from baseline evaluations are requested, they will be calculated for all visits available.

11.4 Methods of safety and tolerability outcome analysis

For safety analyses, the safety analysis set (SAF) will be used.

11.4.1 Adverse events

11.4.1.1 Definitions

For specific regulations of documentation of adverse events (AEs), please refer to the study protocol.

Coding: All AEs reported in this study will be coded using MedDRA Version 23.0.

Timing of AEs: The observation period for an individual subject will start after giving informed consent and will finish at the end of the designated follow-up period. Any medical and surgical event that occurred between Screening Visit and Visit 1 (before the first dose has been administered) will be recorded as medical history. Adverse events that have a start date and time after the first treatment administration are treatment-emergent adverse events (TEAE). In contrast to this, non-treatment emergent adverse events are the ones starting at or after the date of giving the ICF, but not later than the start date and time of first IMP administration. They will be documented under the medical history. AEs with missing onset date will be classified as treatment-emergent.

Causal relationship: Causal relationship between the occurrence of an AE and the administration of the study drug (IMP) is assessed by the investigator according to classification scheme probable and possible, which is assumed to be related to the IMP. Unrelated and unlikely are assumed to be unrelated. In case of missing relationship or unknown, the AE will be classified as related.

Severity/CTC grade intensity: Severity grading will be done by grades mild, moderate and severe.

Imputation of missing information: not done.

Tabulation: All AE tabulations will be presented by treatment group.

Listings: Listings will be prepared showing all adverse events, all MedDRA coding details, all deaths and other serious adverse events. A further listing will be prepared for subjects who experienced any injection site reactions, showing all injection site reaction related information, e.g. site, size, kind of site reaction (redness, itching, pain and plaster used) with its corresponding durations.

Counting of AEs: AE frequency counts will be based on MedDRA coded terms in the overview and frequency tables. Due to a possible splitting of AE verbatims into several MedDRA codes this might lead to a higher number of adverse events compared to the AEs entered in the eCRF. The overview table will therefore display reported adverse event number as noted in the eCRF for additional information as well.

11.4.2 Adverse event summary table

An overview AE summary table will be prepared showing the number and percentage of subjects with at least one event and the total number of events for the following selections:

- Reported TEAEs as noted in the eCRF
- MedDRA coded preferred terms of TEAEs
- MedDRA coded preferred terms of study drug-related TEAEs (ADRs)
- MedDRA coded preferred terms of serious TEAEs (SAEs)
- MedDRA coded preferred terms of study drug-related serious TEAEs (serious ADRs)
- MedDRA coded preferred terms of injection site reactions
- MedDRA coded preferred terms of TEAEs with death as outcome
- MedDRA coded preferred terms of TEAEs leading to study withdrawal

11.4.3 Adverse event frequency tables

In addition, frequency tables will be prepared stratified by MedDRA terms (SOC, PT) showing the following:

Treatment-emergent adverse events (TEAEs):

1. All TEAEs by system organ class and preferred term
2. TEAEs by intensity/severity grading
3. TEAEs by causal relationship to study drug
4. Study-drug related TEAEs (ADRs)
5. Serious TEAEs (SAEs)
6. Serious study-drug related TEAEs (serious ADRs)
7. All injection site reactions
8. All injection site reactions by intensity
9. All injection site reactions – onset time and resolution

For the time to onset (hrs) and time to resolution (since last injection, hrs), a descriptive summary table will be created. No imputation of times in case of missing start and end date/times is done.

The analysis of AEs will include summary tables displaying counts and percentages of subjects experiencing adverse events by SOC and PT. If a subject has more than one AE which codes to the same preferred term, the subject will be counted only once for that preferred term. The total number of events documented per SOC and PT will also be displayed.

Figures: For TEAEs with an incidence rate ≥ 10% a horizontal bar chart will be prepared differing by treatment groups in color. TEAEs will use PT code for display on y-axis.

11.4.4 Global assessment of tolerability

Global assessment of tolerability will be tabulated with counts/percentages by visit and for each treatment group.

11.4.5 Physical examination: Body height and weight, BMI

Body height, weight, the body mass index (BMI, kg/m²) - as calculated out of body height and body weight – and corresponding change from baseline values for weight will be tabulated with descriptive statistics for all visits available and for each treatment group.

11.4.6 Physical examination: Body systems

Number of subjects with normal/abnormal clinically significant/abnormal not clinically significant findings will be tabulated with counts/percentages for all visits available by treatment group.

11.4.7 Vital signs: Blood pressure, heart rate, body temperature and respiratory rate

Details of vital signs (systolic and diastolic pressure (mmHg), heart rate (bpm) in each sitting and standing position, body temperature (°C) and respiratory rate (breaths/min)) will be evaluated by displaying descriptive statistics for each treatment group and time point/visit.

Change from baseline for blood pressure, heart rate, temperature and respiratory rate will be calculated as well and tabulated with descriptive statistics.

11.4.8 Neurological examination

Number of subjects with normal/abnormal clinically significant/abnormal not clinically significant findings by treatment group will be tabulated with counts/percentages for each visit available.

11.4.9 Suicidal ideation/behavior

11.4.10 General questions on suicidal ideation/behavior

The four questions on suicidal ideation/behavior will be displayed for each treatment group and visit by counts/percentages.

11.4.11 Columbian-Suicide Severity Rating Scale (C-SSRS)

If the answer to any of the general questions on suicidal behavior is 'yes', then a further evaluation with the Columbian-Suicide Severity Rating Scale (C-SSRS) is necessary.

The C-SSRS consists of an overview question part on suicidal ideation, which then leads to sub-parts ‘intensity of ideation’ and ‘suicidal behavior’ depending on the answers given. First questions 1 and 2 of the overview part are asked. If both are negative, then it is proceeded to the ‘suicidal behavior’ section, if the answer to question 2 is ‘yes’, then questions 3, 4 and 5 of the overview question part are asked. If the answer to question 1 and/or 2 is ‘yes’, the ‘intensity of ideation’ sections are completed.

The four overall questions concerning suicidal ideation/behavior (C-SSRS) will be evaluated by counts/percentages for each visit. All other answers on subsequent questions concerning suicidal ideation/behavior will be listed on a subject and visit basis.

11.4.12 12-lead ECG (Electrocardiogram)

Number of subjects with normal/abnormal clinically significant/abnormal not clinically significant/unable to evaluate findings in local reading will be tabulated with counts/percentages by treatment group for each visit available.

Further on, the following will be evaluated (data from ERT):

Descriptive analysis of ECG parameters
Results of ECG at each visit will be tabulated with absolute counts and percentages for the variable ECG diagnosis and with descriptive statistics for variables RR (ms), PR (ms) interval, QRS (ms) interval and QT interval (ms).

Analysis of tendency of QTcF/QTcB interval

Absolute values and change from baseline QTcF/QTcB interval for each visit will be presented with descriptive statistics.

Categorical analyses of QTcF/QTcB interval

Categorical analyses of QTcF/QTcB interval data are based on the number and percentage of subjects meeting or exceeding some predefined upper limit value.

The limits are defined as follows:

→ Absolute QTc interval prolongation:

- QTc interval > 450ms
- QTc interval > 480ms
- QTc interval > 500ms

→ Change from screening in QTc interval:

- QTc interval increases from screening ≥30ms
- QTc interval increases from screening ≥60ms

Frequency tables showing the absolute and relative frequency for each category per treatment group and visit will be prepared.

In addition, the maximal QTc prolongation, respectively the maximum change from baseline over time will be used for classification into the above categories and results will be displayed in tabulation by treatment group.

In the ECG external data transfer set, ECG repetitions are referenced as unscheduled visits with repetition number 1, 2 etc. In such cases, ECG repetitions will be included in the listing as well.

All other variables delivered by ECG will be listed.

11.4.13 Clinical laboratory

11.4.13.1 General

- High (H or +)/ Low (L or -) flags will be presented in laboratory listings, where appropriate. If normal values are not available, the flagging cannot be performed.
- All data will be listed in the clinical study report as raw data. Only for the summaries, the most recent value will be used in case several measurements have been performed at one visit.

Tabulations will be prepared for each laboratory parameter:

1. Laboratory result with continuous variables will be presented with descriptive statistics for each scheduled time point. They will be marked whether they are below (low), within (normal) or above (high) the respective reference range.
2. If laboratory values are categorical, the results (e.g. positive/ negative) will be presented with counts and percentages for each visit available.
3. Clinical significance (abnormal not clinically significant NCS and abnormal clinically significant CS) will be evaluated as well for selected parameters (ESR und inflammatory markers in CSF).

11.4.13.2 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

Results of those screening tests will be tabulated according bullet points 1. to 2./sec. 11.4.13.1 General. Summary statistics of absolute values as well as number of values in the reference range or being CS/NCS will be displayed in the same tabulation.

For analysis of blood pregnancy test see sec. 11.4.13.7.

11.4.13.3 Central laboratory: Hematology, clinical chemistry

Tabulation will follow the presentation as suggested above under 1. to 2./ sec. 11.4.13.1 General. Summary statistics of absolute values as well as number of values in the reference range will be displayed in the same tabulation.

The change from baseline values will be calculated for **all** laboratory parameter.

No shift tables will be prepared. In addition to listings presenting all laboratory results, separate listings for the subset of results outside normal ranges will be prepared.

11.4.13.4 Central laboratory: Coagulation

Coagulation parameters (PT (INR), PTT) (LP subgroup, for whom CSF samples are collected) will be evaluated at Screening Visit and Visit 16 (week 48). For those two time points, analyses like for the hematology and clinical chemistry will be conducted.

11.4.13.5 Central laboratory: Biochemistry evaluation of urine samples

Urinalysis parameters (pH, protein, glucose, ketones, blood) will be evaluated like hematology/clinical chemistry with descriptive statistics including change from baseline analyses for continuous parameters and counts/percentages for categorical parameters.

11.4.13.6 Central laboratory: Immunology - Immunoglobuline G

Immunoglobulin G will be evaluated like hematology/clinical chemistry with descriptive statistics including change from baseline analyses.

11.4.13.7 Urine strip tests and blood pregnancy test

Performance of pregnancy test (strip tests) and results of pregnancy test will be listed. Blood pregnancy test (betaHCG) being performed at screening only will be presented in this listing as well.

11.4.13.8 ApoE genotyping

ApoE genotyping results will be listed. ApoE results consist in three polymorphisms (ApoE2 ε2 allele 2, ApoE3 ε3 allele 3 and ApoE4 ε4 allele 4), and single reaction any of the six following genotypes of homozygous type ε2/ε2, ε3/ε3, ε4/ε4 and heterozygous type: ε3/ε4, ε4/ε2, ε2/ε3.

For further analyses of the data subjects will be grouped into ApoE4 (allele 4) carriers and ApoE4 non-carriers. ApoE4 (allele 4) carriers are all those subjects with polymorphism ε4 with a single reaction to genotypes ε4/ε4, ε3/ε4 and ε4/ε2. Non-carriers are genotypes ε2/ε2, ε3/ε3 and ε2/ε3. It is hypothized that carriers of ApoE4 are of increased risk of developing Alzheimer's diseases and response on treatment may differ between those carriers and non-carriers.

Figures

Figures will provide further exploratory insight in correlation structure to certain other investigated parameters using line charts by time (presenting mean value, 95% confidence interval, except for biomarkers for which the median will be shown). Figures will differentiate between subgroups of subjects with the ApoE allele 4 (ApoE4) and without ApoE allele 4. The figure will also distinguish between treatment groups (cohort 1 and cohort 2 (pooled) vs placebo (pooled)), whereas a panel display will be used to show treatment groups side by side. The following parameters will be investigated:

- Biomarkers in plasma (Aβ1-42, Aβ1-40, total tau)
- Biomarkers in serum (NfL)
- Biomarkers in CSF (Aβ1-38, Aβ1-42, total tau, phospho-tau, NfL and Neurogranin)
- CANTAB scores (MOT, RTI or PAL)
- Total BPT score
- VABS-II transformed domain standard scores 1-3.
- Total NPI score and caregiver distress total score (continuous)
- Volumetric MRI percent change atrophy parameters (by location and laterality)

11.4.13.9 Inflammatory markers in blood and CSF

11.4.13.9.1 Inflammatory markers in blood

CRP and ESR in blood will be measured as part of the routine biochemistry evaluation. Both parameters will be analyzed according to the table layout for hematology and clinical chemistry, however for ESR clinical significant (CS) and clinical not significant (CNS) evaluations (bullet point 3./ sec. 11.4.13.1 will be added). Change from baseline analyses will be provided as well with descriptive statistics.

11.4.13.9.2 Inflammatory markers in CSF

CSF samples will be collected in a subgroup of subjects (LP subgroup) and will be obtained by lumbar puncture at Baseline Visit 1 (week 0) and Visit 17 (week 50).

Evidence of inflammation will be examined using differential red blood cell count, white blood cell count, protein, albumin, CSF/serum albumin ratio (if calculated by the site, this has to be re-calculated; if calculated by the EDC, then EDC value is used), IgG index, oligoclonal bands (present/absent) and glucose levels. Data will be presented in listings, including the change from baseline (except for oligoclonal bands) for the second visit.

11.4.14 MRI

Number of subjects with normal/abnormal clinically significant/abnormal not clinically significant/unable to evaluate findings in local reading will be tabulated with counts/percentages for each visit available.

External data for micro hemorrhages and edema will be listed.

11.4.15 Previous and concomitant medication

Previous and concomitant medication will be coded according to WHO-Drug Dictionary DDE 2016-Q1.

The assignment of a medication to previous or concomitant will then be done as follows:

- Partial dates will be imputed. For details on imputation rules, refer to sec. 9
- If imputed onset date or imputed end date >= date of the first drug administration, then the medication is classified as concomitant medication.
- If imputed end date of the medication < date of first drug administration, the medication is classified as previous medication.
- If there is no imputed start or end date for classification, but a variable for an "ongoing" status is available suggesting the medication was ongoing at the end of the study, the medication is classified as concomitant.

Previous and concomitant medication will be presented in separate tabulations by treatment group, by preferred term (PT) and therapeutic class (ATC 2).
All details of previous and concomitant medication will be listed. A separate listing showing the WHO ATC coding details (ATC class 2 + 4) will be prepared. Previous and concomitant medication will be flagged as such in the listing.

12 ANALYSES OF BIOLOGICAL OUTCOME

For biological assessment analyses, the analysis sets mITT and PP will be used.

12.1 Biological endpoints

The following biological endpoints are investigated:

1. Anti-Aβ1-42 Ig antibodies
    a. The primary biological endpoint consists of the anti-Aβ1-42 Ig antibodies in serum.
    b. Secondary biological endpoint consists of anti-Aβ1-42 Ig antibodies in CSF (optional).
2. (Volumetric) MRI of whole brain, ventricle and hippocampal volume
3. T-cell activation
4. Biomarkers including Aβ levels, total tau, phospho-tau, NfL and Neurogranin in plasma and/or in CSF
5. Inflammatory cytokines in plasma and/or in CSF (as noted in the protocol, see also comments in sec. 15.1 Changes to endpoints)
6. Angiogenic proteins and vascular injury markers in plasma and/or in CSF

12.2 Baseline values

Baseline values are the ones measured shortly before the administration of the immunization treatment. This is in most cases the Visit 1 (week 0), except MRI, which has no measurements at Visit 1 but at Screening Visit. For antibody titers the procedure is more complex and described in sec. 12.4.1.

12.3 Calculation of change from baseline/ percent change from baseline

If change from baseline or percent change from baseline evaluations are requested, they will be calculated for all visits available.

12.4 Methods of biological endpoint analyses

12.4.1 Primary biological endpoint: Anti-Aβ1-42 IgG titer in serum

Free anti-Aß IgG in human serum as well as anti-Aß IgG complexed with Aß were measured. The primary endpoint displays results of free anti- Aß IgG titer only. Data will

contain a "result 1" and a "result 2". The data of "result 1" for a given sample should be used for analysis if no data at "result 2" are available. If data are available at "result 1" and "result 2" for a given sample, only the data at "result 2" should be considered for the analysis.

Data imputations:

For evaluation of values below the limit of quantitation (=BLQ values) (tables and figures), the following conventions will be made:

- All concentration values marked as BLQ will be set to 0.5*LLOQ
- Missing post-dose values will not be replaced.

Pre-treatment value/baseline titer value

- In case the anti-Aβ1-42 Ig antibody titer for one sample is BLQ, 0.5*LLOQ will be considered as titer.
- If anti-Aβ1-42 Ig antibody titer at Screening Visit and Visit 1 (before first immunization) are both available, the mean of titer values will be used as baseline value.
- If only one of the values of Screening Visit or Visit 1 (week 0) is available, the single available value will be considered as the pre-treatment value
- If none of the values of Screening Visit or Visit 1 (before first immunization) is available, no pre-treatment value will be assigned to the subject

Definition of response:

A threshold factor was defined during the validation of the free anti-Aß 1-42 IgG in human serum assays (called 'free MSD') and in the validation of the assay for the detection of immune complexes (called 'complexed MSD'). The threshold factor was determined to be equal to 2.80 for free MSD and 1.59 for complexed MSD.

A positive response corresponds to a measured anti-Aβ1-42 IgG titer at or above the baseline/pretreatment titer value multiplied by the threshold factor (2.80 for the free MSD assay and 1,59 for the complexed MSD assay).

A positive responder is a subject having a positive response at any time point after the first immunization in the free MSD assay, as defined above.

Tabulations

All tabulations will show results for free MSD and complexed MSD separately.

No inferential statistical testing will be performed.

Number/proportion of subjects showing a positive antibody response at each visit and at any time point before Visit 11 (week 26) and any time point before Visit 18 (week 52) will be presented with counts/percentages.

For visit specific presentation of results, the value of screening, the value of Visit 1 and the mean of both (assigned to as Baseline visit) will be shown in all tabulations.

Descriptive statistics of the antibody titer will be presented by treatment group for each visit. Besides other descriptive statistics the geometric mean will be shown in this tabulation.

Change from baseline and percent change from baseline will be presented as well with descriptive statistics by treatment group for each visit, but without presenting results with geometric mean.

Tabulation of descriptive measures of the area-under-the curve (AUC): For each subject 2 different AUCs will be calculated. AUC calculation is based on change from baseline results. Descriptive statistics per treatment group of each of the AUC will be displayed.

Separate AUC will be calculated as:

- AUC (Week 0 - Week 52)
- AUC (Week 0 - Week 96)

Nominal times rather than actual time pointed will be used for AUC calculation.

AUC will be displayed in [AU/ml/wks.].

Figures

All figures will show results for free and complexed MSD method separately.

For all figures arrows will indicate drug administration time points.

- Figures of the absolute mean titers (mean ± 95% confidence limits) per treatment groups; the 0.5*LLOQ will be presented as a separate line and time points of immunization marked.
- Figures of the absolute geometric mean titers (no confidence limits) per treatment groups; the 0.5*LLOQ will be presented as a separate line and time points of immunization marked.

- Figures of mean change from baseline per treatment group. Time points of immunization will be marked.
- Figures of mean percent change from baseline per treatment group.
- Individual figures of antibody (positive results and imputed BLQ) titer (AU/ml) for each subject (using linear scale of y-axis):
    - One figure per treatment group: All subjects belonging to a treatment group will be plotted in one figure (absolute titer of anti-Abeta IgG).
    - Individual figures per subject: Single figures for absolute values of IgG for each subject will be provided.
    - Individual figures per subject: Single figures for change from baseline values of IgG for each subject will be provided
    - Individual figures per subject: Single figures for percent change from baseline values of IgG for each subject will be provided

- Correlation analyses of treatment group absolute mean and individual antibody values of anti-Aβ1-42 IgG at each time point (linear scale for antibody values) by treatment group using a line plot.
  The line plot will display:
  - Left y axis: Anti-Aβ1-42 IgG (separately for free and complexed MSD method)
  - Right y axis: absolute value of each biomarker or each rating scale
  - x axis: time
  - 2 lines in one graph
  - For individual IgG data per subject: 2 panel per subject putting each biomarker in plasma/serum+ CSF) into one panel
  - For treatment group mean IgG data: one page per treatment group (cohort 1/cohort 2/pooled Placebo), but using a panel putting each group of biomarkers plasma/ serum+ CSF) into one panel

  The following parameters (individual per subject) will be compared using individual graphs (one figure per subject):

    - Antibody value versus each biomarker in plasma (Aβ1-42, Aβ1-40, total tau) and serum (NfL)
        - Antibody value versus each biomarkers in CSF (Aβ1-38, Aβ1-42, total tau, phospho-tau, NfL and Neurogranin)
        - Antibody value versus CANTAB (MOT, RTI or PAL)
        - Antibody value versus BPT score
        - Antibody value versus VABS/II transformed domain standard scores 1.-3.
        - Antibody value versus total NPI total score

- Antibody value versus caregiver distress total score (continuous)
- Antibody value versus volumetric MRI percent change atrophy parameters (by location and laterality)
- Antibody value versus BMI

In addition, the following parameters (per treatment group) will be compared using treatment group mean graphs (one figure per treatment group):

- Antibody value against each biomarkers in plasma (Aβ1-42, Aβ1-40, total tau) and serum (NfL)
- Antibody value against each biomarkers in CSF (Aβ1-38, Aβ1-42, total tau, phospho-tau, NfL and Neurogranin)

For antibody values correlation inspection by age group, individual line plots will be prepared:

- Antibody values by age groups using a median split (median age (≥ median, < median) derived from all subjects in cohorts 1, 2 and placebo).

12.4.2 Anti-Aβ1-42 IgM titer in serum

Data imputations:

For evaluation of values below the limit of quantitation (=BLQ values) (tables and figures), the following conventions will be made:

- All concentration values marked as BLQ will be set to 0.5*LLOQ
- Missing post-dose values will not be replaced.

Pre-treatment value/baseline titer value

- If anti-Aβ1-42 IgM antibody titer at Screening Visit and Visit 1 (before first immunization) are both available, the mean of titer values will be used as baseline value.
- If only one of the values of Screening Visit or Visit 1 (week 0) is available, the single available value will be considered as the pre-treatment value
- If none of the values of Screening Visit or Visit 1 (before first immunization) is available, no pre-treatment value will be assigned to the subject

Positive response:

Note that there is no threshold for IgM and therefore no responder, can be derived.

Analyses for anti-Aβ1-42 IgM titer in serum will then comprise only selected tabulations.

Tabulations

All tabulations will show results for ELISA method.

Descriptive statistics of the antibody titer will be presented by treatment group for each visit. The geometric mean will be shown in this tabulation as well.

Changes from baseline will be tabulated with descriptive statistics for visits

12.4.3 Secondary biological endpoint: anti-Aβ1-42 Ig titer in cerebrospinal fluid (CSF)

No CSF samples are available for this analysis, therefore no Aβ1-42 Ig titer values in CSF will be evaluated.

12.4.4 Volumetric MRI/PET Imaging

vMRI:
Descriptive statistics for all volumetric MRI results for each visit/location/laterality will be tabulated for each treatment group. As atrophy is already measured as a change from baseline (CHG) value no additional change from baseline derivation has to be done. However based on atrophy results the percent change will be derived in addition (PCHG = (atrophy value/volume at baseline)*100) for each visit/location/laterality and both will be tabulated.

Figures:
Mean (and 95% confidence interval) for all volumetric percent change atrophy MRI parameters will be displayed with a line plot over time for each treatment group. Line plots will differ between location and laterality.

PET Imaging:
As per protocol v.3.0 (amendment 2), PET exams are not performed anymore, however as PET data recordings up to that amendment have been done, the available data will be listed.

12.4.5 Blood T-cell activation (IFN-γ and IL-4 release by T-cells)

T-cell activation cytokine levels will be tabulated with descriptive statistics by treatment group for each visit. Changes from baseline will be tabulated with descriptive statistics for visits.

Figures:
Figures will show results of IFN-γ and IL-4 release separately for each time point via line plot. Separate plots for absolute values, change from baseline and percent change from baseline values will be created.

12.4.6 Biomarkers (Aβ1-42, Aβ1-40, total tau) in plasma, NfL in serum and biomarkers (Aβ1-38, Aβ1-42, total tau, phospho-tau, NfL and Neurogranin) in CSF

Biomarkers including Aβ levels (e.g. Aβ1-42, Aβ1-40, Aβ1-38, ratio Aβ1-42/Aβ1-40), tau proteins (total tau, phospho-tau (only for CSF)), Neurogranin and NfL will be descriptively evaluated by treatment group for each visit. Changes from baseline will be tabulated with descriptive statistics for visits.

Tabulations will differ between biomarkers in plasma, serum, and CSF.

Figures:
Figures will show Aβ1-42, Aβ1-40, Aβ1-38, ratio Aβ1-42/Aβ1-40, tau proteins (total tau,), Neurogranin and NfL. Time points of immunization will be marked:

- Box plots of biomarkers in plasma, serum, and CSF per visit and treatment group. Mean will be dismissed in the figure.
- Mean (and 95% confidence interval) of absolute results for biomarkers in plasma/ serum/ CSF will be displayed with a line chart over time for each treatment group.
- Mean (and 95% confidence interval) of change from baseline results for biomarkers in plasma/ serum/ CSF will be displayed with a line chart over time for each treatment group.
- Mean (and 95% confidence interval) of percent change from baseline results for biomarkers in plasma/ serum/ CSF will be displayed with a line chart over time for each treatment group.
- Individual absolute results of biomarkers in plasma /serum/ CSF for each subject in treatment-specific separate graphs (line graph).

- Individual change from baseline results of biomarkers in plasma /serum/ CSF for each subject in treatment-specific separate graphs (line graph).
- Individual percent change from baseline results of biomarkers in plasma /serum/ CSF for each subject in treatment-specific separate graphs (line graph).

12.4.7 Angiogenic proteins and vascular injury markers in plasma

Angiogenic proteins including basic FGF, PIGF, Flt-1, Tie-2, VEGF, VEGF-C, VEGF-D, and vascular injury markers including SAA, CRP, VCAM-1, ICAM-1 will be descriptively evaluated by treatment group for each visit. Changes from baseline will be tabulated with descriptive statistics for visits.
For each angiogenic protein and vascular injury parameter, figures as in the section 12.4.6 will be prepared except the boxplots.

12.4.8 Inflammatory cytokines in serum

Inflammatory cytokines including IFN-γ, IL-1β, IL12p70, IL-10 and TNF-α will be descriptively evaluated by treatment group for each visit. Changes from baseline will be tabulated with descriptive statistics for visits.
For each inflammatory cytokine, figures as in the section 12.4.6 will be prepared except the boxplots.

13 EFFICACY ANALYSES

13.1 Efficacy endpoints

Efficacy assessments will comprise the evaluation of:

1. Change from baseline measured by Clinical Global Impression of Change (CGIC)
2. Cognitive functions as measured by the
    a. Change from baseline in Cambridge Neuropsychological Test Automated Battery (CANTAB)
    b. Change from baseline in Brief Praxis Test (BPT)
3. Clinical rating scale assessments as measured by the
    a. Change from baseline in Vineland-II Adaptive Behavior Scale (VABS-II)
    b. Change from baseline in Neuropsychiatric Inventory (NPI)

13.2 Baseline values

Unless not otherwise noted, baseline is defined as the value recorded prior to the first application, which is Visit 1 (week 0).

13.3 Calculation of change from baseline

If change from baseline evaluations are requested, the change of all available visits will be calculated.

13.4 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 may be postponed until the time of the next interim analysis of cohort 2, which is planned at Visit 12 [week 28].

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 (part of biomarker data). Interim analyses at Visit 12 [week 28] and Visit 18 [week 52] will additionally include biomarkers, CGIC, NPI and Vineland data (part of clinical rating scales and cognitive tests). Since antibody titer and biomarker data are potential unblinding data, those additional interim analyses will be unblinded by group, but blinded as to individual subject numbers, i.e. individual subject numbers will be recoded – this semi-blinded data will ONLY be presented to the sponsor's steering committee, who does not have access to clinical data (and unblinded individual subject numbers). Tables and listings to be prepared for interim analyses will be indicated in sections 16.3.

In addition to these interim analyses, biological effects analysis (except whole brain, ventricle and hippocampal volume) is assessed periodically to gain preliminary information concerning assay functionality and biological effects and to assist in safety assessments as needed.

The additional interim analyses will be applied for the ALL, SAF or mITT population as appropriate. For each interim analysis a cut-off date will be agreed with the sponsor, up to which entries in the DB have to be respected.

13.5 Examination of subgroups

N/A

13.6 Multiple comparison/ multiplicity

No adjustments concerning multiple testing will be done.

13.7 Multicenter studies

This is multi-center study, originally planned to have six centers in the United States participating in the study. Finally 4 active sites took part to the study and only 3 sites have been enrolling. This leads to only few subjects per center, for this reason no center adjustment for specific analyses will be included in the statistical analysis plan.

13.8 Methods of efficacy analysis

For analyses of the efficacy parameters, the mITT and PPS will be used.

13.8.1 Clinical Global Impression of Change (CGIC)

The clinical global impression of change will ask whether the status compared to baseline is 'marked improvement' (1), 'moderate improvement' (2), 'minimal improvement' (3), had 'no change' (4), is 'minimal worsening' (5), 'moderate worsening' (6) or 'marked worsening' (7).

For each visit available, descriptive statistics for the CGIC (interpreting CGIC as continuous variable) and counts/percentages for the CGIC will be displayed by treatment group.

No change from baseline evaluations will be done as the CGIC already presents changes.

Figures: All figures will include arrows at timepoints of immunization.

- For each treatment group, the absolute mean CGIC per visit will be displayed with the SEM using a line chart.

13.8.2 Cambridge neuropsychological test automated battery (CANTAB)

The CANTAB is a computer-based cognitive assessment system consisting of a battery of neuropsychological tests, administered to subjects using a touch screen computer. The 25 tests in CANTAB examine various areas of cognitive function, including general memory and learning, working memory and executive function, visual memory, attention and reaction time (RT), semantic/verbal memory, decision making and response control.
The tests selected from this battery for this study are as follows: Motor control (MOT), reaction time (RTI) and paired associated learning (PAL).

The analysis of CANTAB results will comprise:

- A tabulation of each of the CANTAB test results (MOT, RTI and PAL) by visit and treatment group using descriptive statistics.
- A change from baseline tabulation comparing each of the CANTAB baseline score values of Visit 1 to further visits using descriptive statistics.
- Figures: All figures will include arrows at timepoints of immunization.
    - Mean CANTAB MOT, RTI or PAL score (± SEM) per visit by treatment group using a line plot.
    - For each MOT, RTI and PAL score separately: Mean change from baseline values (± SEM) per visit by treatment group using a line plot.
    - Individual figures of CANTAB test results (MOT, RTI and PAL) by median split KBIT-2 score (based on all cohort 1, 2 and placebo subjects) and by

treatment group. The display of treatment groups will use a panel display and will differ between certain groupings of treatment:

- Cohort 1 vs cohort 2 vs Placebo (pooled)
- Responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)
- Responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)
- Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo (pooled)

13.8.3 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

RBANS provides a brief, individually administered battery to measure cognitive decline or improvement across 5 domains with the aid of 12 subset tests. For this study 7 selected subtests have been chosen:

Domain	***Subtest***	***Points***	***Raw domain scores***	***Index domain scores***	
1. Immediate memory	Subtest 1: List learning Subtest 2: Story memory	0-40 0-24	0-64		
2. Visuospatial/ constructional	Subtest 3: Figure Copy Subtest 4: Line Orientation	0-20, Not included in the eCRF 0-20, Not included in the eCRF	0-40		
3. Language	Subtest 5: Picture naming Subtest 6: Semantic fluency	0-10 0-40	0-50		
4. Attention	Subtest 7: Digit span	0-16	0-105		
	Subtest 8: Coding	0-89, Not included in the eCRF			
5. Delayed memory	Subtest 9: List recall Subtest 10: List recognition	0-10 0-20	0-62		
	Subtest 11: Story Recall Subtest 12: Figure Recall	0-12, Not included in the eCRF 0-20, Not included in the eCRF			
				Sum of index scores	Total Scale Score

The points, and total scale score will be entered in the eCRF by the investigators. As per protocol v4.0 (amendment 3) no RBANS evaluations will be done anymore and the secondary endpoint referring to the evaluation of RBANS was skipped. Data collected up to this amendment will be listed.

13.8.4 Brief praxis test (BPT)

The Brief Praxis Test (BPT) measures performance ability in the following areas: Psychomotor skills while standing, psychomotor skills while seated, apraxia and body parts/ coin task. In each of those areas several tasks have to be fulfilled, for which each grade of completing gets different points:

Dimension	***Question***	***Points***
1. Psychomotor skills while standing	Walk towards me. 1. Clap your hands	*Not in eCRF. Instruction what the person should do.*
	2. Lift one arm over your head 3. Lift the other arm over your head. 4. Turn your head to one side. 5. Turn your head to the other side. 6. Lift one leg. 7. Lift the other leg.	1-4 points
2. Psychomotor skills while seated	8. Place each of the coins inside the jar. 9. Place each of the coins inside the jar with the other hand. 10. Scratch your head. 11. Snap your fingers.	1-4 points
3. Apraxia	12. Salute. 13. Open the jar. 14. Close the jar. 15. Unlock the padlock. 16. Lock the padlock.	1-4 points
4. Body parts/ coin task	17. Point to your index finger.	0 or 4 points
	Coin test 1: Give me a penny.	*Not in eCRF. Instruction what the person should do.*
	18. Coin test 2: Please give me a nickel.	0 or 4 points
	19. Coin test 3: Please give me a quarter.	0 or 4 points
	20. Coin test 4 Please give me a dime.	0 or 4 points

4 points: Correct response on request without any additional verbal prompts, imitation, or modeling, or any form of physical assistance by the examiner.
3 points: Successful performance by the individual after the use of verbal prompts.
2 points: Successful performance by the individual following a modeling prompt.

1 point: Successful performance by the individual following a physical prompt.
0 points: Unable or unwilling to perform the required item.

The dimension points can be entered in the eCRF by the investigators. These entries will be used for further analyses. A total BPT score will be derived by simply summing up all single questions. The score can be derived in case all questions have been answered.

The analysis of BPT results contains:

- A tabulation of each question and the total BPT score by visit and treatment group using descriptive statistics.
- A change from baseline tabulation comparing each question and the total BPT score of Visit 1 to further visits using descriptive statistics.
- Figures: All figures will include arrows at timepoints of immunization.
    - For total BPT score, the mean value (± SEM) per visit by treatment group using a line plot.
    - Mean total BPT score change from baseline values (± SEM) per visit by treatment group using a line plot.
    - Individual figures of total BPT score by median split KBIT-2 score and by treatment group. The display of treatment groups will use a panel display and will differ between certain groupings of treatment:
        - Cohort 1 vs cohort 2 vs Placebo (pooled)
        - Responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)
        - Responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)
        - Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo (pooled)

13.8.5 Vineland-II adaptive behavior scale (VABS-II)

The Vineland Adaptive Behavior Scales, Second Edition (Vineland-II, VABS-II) measures the personal and social skills of individuals from birth through adulthood. Because adaptive behavior refers to an individual's typical performance of the day-to-day activities required for personal and social sufficiency, these scales assess what a person actually does, rather than what he or she is able to do. The Vineland-II assesses adaptive behavior in four domains: Communication, daily living skills, socialization, and motor skills. For this study 3 selected domains have been chosen (communication, daily living skills, socialization). Motor skills will not be evaluated. Therefore, a composite score that summarizes the individual's performance across all four domains will not be calculated. The maladaptive behavior index is optional and can be used depending on the site. For this reason the maladaptive behavior index will only be listed and not tabulated.

In order to determine the level of an individual's adaptive behavior, someone who is familiar with that individual, such as a parent or caregiver, is asked to describe his activities. Those activities are then compared to those of other people the same age to determine which areas are average, above average, or in need of special help.

Domain	***Subdomain***	***Result (Raw score)***	***v-scale score***	***Transformed domain standard score***
1. Communication	1.1 Receptive 1.2 Expressive 1.3 Written	xx xx xx	xx xx xx	xx
2. Daily living skill	2.1 Personal 2.2 Domestic 2.3 Community	xx xx xx	xx xx xx	xx
3. Socialisation	3.1 Interpersonal relationships 3.2 Play and leisure time 3.3 Coping skills	xx xx xx	xx xx xx	xx
4. Motor skills	4.1 Fine 4.2 Gross	N/A in this trial.		
5. Maladaptive Behavior Index (optional)	5.1 Internalizing 5.2 Externalizing	xx xx	xx xx	

Raw scores for each subdomain, except motor skills, the v-scale scores for each subdomain and the transformed domain standard scores for domains 1.-3. can be entered in the eCRF by the investigators.

Transformed domain standard scores 1.-3. can be further interpreted according to tabled values as high (130 and above), moderately high (115-129), adequate (86-114), moderately low (71-85), and low (70 and below). Domain standard scores will therefore be categorized as well.

Analysis:

The analysis of VABS-II results is as follows:

- A tabulation of the v-scale scores of each subdomain by visit and treatment group using descriptive statistics.

- A tabulation of the transformed domain standard scores 1.-3. by visit and treatment group using descriptive statistics. Further on the domain standard scores will be presented in a categorized manner and presented with counts/percentages in the same table.
- A change from baseline tabulation comparing each domain standard baseline score value of Visit 1 to further visits using descriptive statistics.
- Figures: All figures will include arrows at timepoints of immunization.
    - Mean domain standard score absolute values (± SEM) per visit by treatment group using a line plot.
    - Mean domain standard score change from baseline values (± SEM) per visit by treatment group using a line plot.
    - Individual figures of transformed domain standard scores 1.-3. by median split KBIT-2 score and by treatment group. The display of treatment groups will use a panel display and will differ between certain groupings of treatment:
        - Cohort 1 vs cohort 2 vs Placebo (pooled)
        - Responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)
        - Responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)
        - Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo (pooled)

13.8.6 Neuropsychiatric inventory (NPI)

Score derivation:

The Neuropsychiatric Inventory (NPI) assesses dementia-related behavioral symptoms. The NPI examines 12 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity, night-time behavioral disturbances and appetite and eating abnormalities.

In case of presence, both the frequency (1: occasionally, 2: often, 3: frequently, 4: very frequently) and severity (1: mild, 2: moderate, 3: marked) of each domain will be determined and multiplied together. In case the domain is not present/ not applicable, frequency, severity and the product of both is set to 0. Missing entries remain missing.

The NPI total score is then calculated by adding the scores of the domains together using the frequency x severity variable. This leads to a total score of 0-144; a higher score indicates more severe psychopathology.
The caregiver distress scores are displayed separately.

Analysis:

Analysis of NPI results:

- A separate tabulation of the NPI total score and the caregiver distress total score (interpreted as discrete and as continuous) by visit and treatment group using descriptive statistics and counts/percentages.
- A change from baseline tabulation comparing each NPI total score and the caregiver distress total score baseline values of Visit 1 to further visits using descriptive statistics.
- Figures: All figures will include arrows at timepoints of immunization.
    - For the caregiver distress scores and the total NPI score, the mean value (± SEM) per visit by treatment group using a line plot.
    - Mean caregiver distress total score and NPI total score in terms of change from baseline values (± SEM) per visit by treatment group using a line plot.
    - Individual figures of NPI total score and the caregiver distress total score (continuous) by median split KBIT-2 score and by treatment group. The display of treatment groups will use a panel display and will differ between certain groupings of treatment:
        - Cohort 1 vs cohort 2 vs Placebo (pooled)
        - Responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)
        - Responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)
        - Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo (pooled)

14 OTHER SAFETY AND SUPPORTIVE ANALYSES

14.1 Extent of exposure and compliance

Subjects receive their IMP via s.c. injection at Visit 1 (day 0, month 0), Visit 3 (week 4, month 1), Visit 5 (week 8, month 2), Visit 7 (week 12, month 3), Visit 10 (week 24, month 6), Visit 13 (week 36, month 9) and finish at Visit 16 (week 48, month 12). Subjects in cohort 1 should get one injection per visit and subjects in cohort 2 should get two concomitant injections per visit, which will be documented in the eCRF.

An overview table (not visit specific) will show information of general variables concerning study drug administration by treatment group with counts/percentages/descriptive statistics:

- Total number on injections administrated (counts/percentages). Theoretically, subjects in cohort 1 should receive seven injections and in cohort 2 fourteen injections (ie, 7 administration with 2 injections per administration in cohort 2).
- Total dose administered: Cohort 1 will get 300µg antigen per injection (0.75mL), subjects in cohort 2 will get 400µg antigen via first injection (1.0mL), and 600µg antigen via second injection (1.5mL) to gain 1,000 µg in total.
- Average dose administered (dose per visit) (dividing total dose by the number of visits).

Compliance can be evaluated by looking at key variables number of injections administered and average dose administered.

All other information concerning study treatment as entered in the eCRF will be listed.

14.2 Time between visits and total study duration

Visit dates will be listed only.

Time between visits as well as total study duration will be derived and tabulated with descriptive statistics (duration of total study (days) = date of study completion or discontinuation – date of informed consent + 1).

15 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

15.1 Changes to endpoints

According to laboratory documentations (ACI-24-1301_Data file specification_Ver0.4, 24 January 2018, Laboratory QPS) the secondary endpoint 'Inflammatory cytokines in plasma and/or in CSF' is not evaluated in plasma or CSF, but in serum only. Inflammatory cytokines comprise IFN-γ, IL-1β, IL12p70, IL-10 and TNF-α.

15.2 Changes to analyses

SAP is based on protocol version 5.0. In comparison to protocol version 4.0 TLR-4 evaluations have been deleted.
Compared to other previous protocol versions, the evaluation of PET (protocol version 3.0) and RBANS (protocol version 4.0) have been removed. Data collected for these investigations will be listed, but not further analyzed.

16 APPENDICES

16.1 Appendix A: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., µ, a, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes should be used sparingly and must add value to the table, figure, or data listing.

Tables

- Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.
- Means and medians will be presented to one more decimal place than the raw data. Standard deviations will be presented to two more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) should be presented to one decimal place more than the raw/derived data.
- For all inferential analyses, p-values will be rounded to four decimal places (or at the highest level of precision) with a leading zero (0.0001). P-values less than 0.0001 will be presented as "<0.0001".

Figures

- Legends will be used for all figures with more than one variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white (no color) unless colors add value to the clarity and readability of a figure. Lines should be wide enough to see the line after being copied. Legends will be used for all figures with more than one variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Scatter plots will include the regression line if applicable.
- Line graphs over time of change from baseline results will include a horizontal dashed reference line at zero if requested/ specified.
- For box plots, the horizontal line will represent the median, + represents the group mean (if not otherwise specified in the textual part), the length of the box represents the interquartile range (25th-75th percentiles), and the whiskers will represent the minimum and maximum.

Listings

- Formal organization of the listing may be changed during programming if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints, etc.
- If not otherwise specified, all data listings will be sorted by cohort, treatment (ACI-24 300 µg, ACI-24 1,000 µg, Placebo), subject number, visit, and date/time as appropriate.
- All date values will be presented in SAS date or ISO date format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.

16.2 Appendix B: SAS programming QC requirements

Programmer/ validator review

1. **Program Review**
   - **1.1. Program name** follows standard naming conventions and is consistent with other study program names.
   - **1.2. Program header** uses standard template with all relevant information completed.
   - **1.3. Program flow** is logical (i.e., header → initialization code → macro variable definitions → format definitions → main body).
   - **1.4. Programmer comments** are included throughout program to describe purpose of individual sections or macros and provide understanding of specific code, if necessary. All comments are clear and up-to-date.
   - **1.5. Hard coding,** if any, is implemented correctly and documented in program header with: date, reason, and reference to sponsor approval. A comment is also inserted at the location of the hard coding.
   - **1.6. SAP Derivation** rules, if any, are followed. Significant deviations from mock table or SAP text are documented in the SAS Program Header.
   - **1.7. Permanent intermediate datasets** utilized as source data have either been fully validated elsewhere or are fully validated within the scope of this QC.
   - **1.8. Program runs** properly and output dataset is generated as intended.

2. **SAS Log Review**
   - **2.1. Scan of entire log** confirming that each data step and procedure completed properly.
   - **2.2. Critical messages** such as: errors, warnings, merge notes, or uninitialized variables are not found in log. Unavoidable critical messages are verified to not adversely affect the output and the reasons why they are unavoidable are documented.
   - **2.3. Other messages** such as “PUT” or “INFO” messages (e.g., overwritten variables following merge) are handled appropriately, if they are found in log.

3. **Output Review**
   - **3.1. Output file name** follows standard naming conventions and is consistent with other study output file names.
   - **3.2. Titles and footnotes** are verified against mock table/listing/figure (if available). Discrepancies, including footnotes added for clarification, are noted and verified.

3.3. **Column/row header text** is verified against mock table/listing/figure and/or CRF.
3.4. **Format and sorting order** are correct relative to mock table/listings/figure and/or CRF.
3.5. **Pages breaks** are as intended throughout the document.
3.6. **Significant digits** are appropriate for summary results (e.g., mean is one more digit than collected on the CRF, etc.).
3.7. **Analysis population totals** are verified as correct based on SAP definitions and are consistent with other tables using the same population(s).
3.8. **Inappropriate data:** checked for outliers, invalid numbers, missing results, etc.

4. Dataset Structure (for SDTM/TDM/AdaM)

4.1. OpenCDISC validator is run. Any errors or warnings are updated or explained.

5. Verification of Data

5.1. SDTM/TDM/AdaM datasets

5.1.1. Programmer

Each SDTM/TDM/ADaM is opened and data are reviewed for consistency with the protocol, SAP, and/or CRF (no additional QC programming is necessary).

5.1.2. Validator

Full validation is performed against the protocol, SAP, and/or CRF. A spot-check of source data against the output dataset is performed on at least 2 subjects. Each CRF section/form should be populated at least once for the spot-check. If a section/ form is repeated (e.g. at several visits) one repeat per subject has to be spot-checked.

5.2. Tables

5.2.1. Program Review

- Verify that the appropriate datasets, variables, analysis populations, parameters/tests, and visits/time points are used.
- Verify that all keyword and positional parameters of the standardized macro call are accurate and are implemented as intended.

5.2.2. Output Review

- All expected data (parameters/tests, visits/time points, treatments, totals, etc.) are included on the output.
- Units and the range of values are confirmed to be consistent.
- Percentages are based on the correct denominator and confirmed to not exceed 100%.
- Counts within subgroups or subsets of data are checked for internal consistency (e.g., subset counts do not exceed overall counts).

5.3. Listings

- Listing content is as expected (e.g., listing includes all enrolled subjects, all expected visits, etc.)
- Variables directly from source dataset are spot-checked for accuracy and completeness.
- Derived or calculated variables are compared to corresponding source data and manual calculation for at least 2 subjects are done.

5.4. Figures

- Manual comparison to the corresponding table, where the table is validated and at least 25% of the data points on the figure are compared to the corresponding value on the table.
- Manual calculations (if feasible based on small Ns or frequency counts).

6. Documentation

6.1. The Programmer and Validator must document completion of QC (e.g., date of QC and method used) in **BIO-0205-TMP-002 Program Status Document.**

6.2. Validator findings and/or comments may be tracked in the Program Status Document along with a description of how the finding was resolved and resolution date.

6.3. The following must be retained electronically within the study folder by the Programmer as supporting documentation for SDTM and TDM datasets:

- For SDTM/TDM/ADaM, OpenCDISC report generated at time of QC including comments explaining findings.
- For SDTM/TDM/ADaM, OpenCDISC report generated after all QC findings are resolved including comments explaining findings.

6.4. The following must be retained electronically within the study folder by the Validator as supporting documentation:

- If a spot-check of subject data is performed, output that clearly identifies the subjects and CRF forms/sections that are checked

Senior Level Review

1. **Output Package**
   - **1.1. All analysis tables, listings and figures**, as outlined in the SAP are contained in the package. If any are missing, the reason is documented appropriately.
   - **1.2. Dates and times of electronic output files** are consistent with each other and with the corresponding dates of the source data sets.

2. **Database and Documentation**
   - **2.1. File dates of datasets** within the clinical database, SDTM datasets, and analysis datasets are consistent. All clinical database datasets were updated together at the appropriate time, SDTM datasets (if any) were updated following the update of the clinical database, and analysis datasets were updated following the update of the clinical source datasets and SDTM datasets (if any).
   - **2.2. QC of all programs** has been completed by both the Programmer and Validator, as confirmed by **BIO-0205-TMP-002 Program Status Document**.
   - **2.3. All datasets, SAS programs, and SAS program logs** have been saved and are ready for archival.
   - **2.4. The randomization assignments** have been verified to be accurate in all datasets at the time of the final batch run of programs**.**

3. **Output Review**
   - **3.1. Titles are appropriate** and match the corresponding mocks and Table of Contents (if available). Title format and numbering is consistent across all TLFs.
   - **3.2. Footnotes are appropriate** and match the corresponding mocks and Table of Contents (if available). Reference numbers are consistent in format and correspond to the body of the output. Version of output is represented accordingly (e.g., DRAFT designation is removed, if final).
   - **3.3. Formatting is consistent** across all analysis tables, listings, and figures (i.e., case/punctuation in column and row headers, underlining of column headers, page breaks, etc.).
   - **3.4. Invalid data** such as blatant data point errors, outliers, missing data are scanned for in the outputs.
   - **3.5. Population denominators** are consistent across summary tables and figures.
   - **3.6. Potential discrepancies**, if any, found during review have been corrected and/or handled appropriately.

4. Statistical Review

4.1. **The primary efficacy analysis** and any key secondary efficacy or safety analyses are carefully reviewed for consistency and plausibility. Any potential issues are investigated and discussed with the Programmer and/or Biostatistician.

16.3 Appendix C: List of Tables, Figures, and Listings

The following TLF numbering is completed according to ICH guidelines. The ICH heading number and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.

16.3.1 List of tables and figures for final analysis

Header entries are marked bold.

Table/Figure Number	**Table/Figure Description**	**Analysis Set**	**Additional TLF – delivered separately after initial set of TLFs**
14.1	**DEMOGRAPHIC DATA**		
14.1.1	Subject numbers per site	**ALL**	
14.1.2	Subject disposition	**ALL**	
14.1.3	Study closure from/Exit form	**ALL**	
14.1.4	Demographics	**ALL**	
14.1.5	Medical history	**ALL**	
14.2	**EFFICACY**	**mITT, PPS**	
14.2.1	**Clinical global impression of change**		
14.2.1.1	CGIC: Descriptive statistics		
14.2.1.2	Figure: CGIC: Mean untransformed result		
14.2.2	**Cambridge neuropsychological test automated battery (CANTAB)**		
14.2.2.1	CANTAB: Descriptive statistics		
14.2.2.2	CANTAB: Change from baseline		

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.2.2.3	Figure: CANTAB – MOT, RTI, PAL: Mean absolute value		
14.2.2.4	Figure: CANTAB – MOT, RTI, PAL: Mean change from baseline		
14.2.2.5	Figure: Individual CANTAB results (MOT, RTI and PAL) by KBIT-2 score: Absolute value by treatment group		**x**
14.2.2.6	Figure: Individual CANTAB results (MOT, RTI and PAL) by KBIT-2 score: Absolute value by responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)		**x**
14.2.2.7	Figure: Individual CANTAB results (MOT, RTI and PAL) by KBIT-2 score: Absolute value by responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)		**x**
14.2.2.8	Figure: Individual CANTAB results (MOT, RTI and PAL) by KBIT-2 score: Absolute value by Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo (pooled)		**x**
14.2.3	**Brief praxis test (BPT)**		
14.2.3.1	BPT: Descriptive statistics		
14.2.3.2	BPT: Change from baseline		
14.2.3.3	Figure: total BPT score: Mean absolute value		
14.2.3.4	Figure: total BPT score: Mean change from baseline		
14.2.3.5	Figure: Individual total BPT score (MOT, RTI and PAL) by KBIT-2 score: Absolute value by treatment group		**x**
14.2.3.6	Figure: Individual total BPT score (MOT, RTI and PAL) by KBIT-2 score: Absolute value by responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)		**x**
14.2.3.7	Figure: Individual total BPT score (MOT, RTI and PAL) by KBIT-2 score: Absolute value by responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)		**x**
14.2.3.8	Figure: Individual total BPT score (MOT, RTI and PAL) by KBIT-2 score: Absolute value by Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo		**x**
14.2.4	**Vineland-II adaptive behavior scale (VABS-II)**		
14.2.4.1	VABS-II: Descriptive statistics of v-scale scores		
14.2.4.2	VABS-II: Descriptive statistics of domain standard scores		
14.2.4.3	VABS-II: Change from baseline for domain standard scores		
14.2.4.4	Figure: VABS-II domain scores: Mean absolute value		

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.2.4.5	Figure: VABS-II domain scores: Mean change from baseline		
14.2.4.6	Figure: Individual transformed domain standard scores 1.-3. by KBIT-2 score: Absolute value by treatment group		**x**
14.2.4.7	Figure: Individual transformed domain standard scores 1.-3. by KBIT-2 score: Absolute value by responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)		**x**
14.2.4.8	Figure: Individual transformed domain standard scores 1.-3. by KBIT-2 score: Absolute value by responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)		**x**
14.2.4.9	Figure: Individual transformed domain standard scores 1.-3. by KBIT-2 score: Absolute value by Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo		**x**
14.2.5	**Neuropsychiatric inventory (NPI)**		
14.2.5.1	NPI: Descriptive statistics		
14.2.5.2	NPI: Change from baseline		
14.2.5.3	Figure: Caregiver distress total score: Mean absolute value		
14.2.5.4	Figure: Caregiver distress total score: Mean change from baseline		
14.2.5.5	Figure: NPI total score: Mean absolute value		
14.2.5.6	Figure: NPI total score: Mean change from baseline		
14.2.5.7	Figure: Individual caregiver distress total score (continuous) by KBIT-2 score: Absolute value by treatment group		**x**
14.2.5.8	Figure: Individual caregiver distress total score (continuous) by KBIT-2 score: Absolute value by responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)		**x**
14.2.5.8	Figure: Individual caregiver distress total score (continuous) by KBIT-2 score: Absolute value by responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)		**x**
14.2.5.10	Figure: Individual caregiver distress total score (continuous) by KBIT-2 score: Absolute value by Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo		**x**
14.2.5.11	Figure: Individual NPI total score by KBIT-2 score: Absolute value by treatment group		**x**
14.2.5.12	Figure: Individual NPI total score by KBIT-2 score: Absolute value by responder cohort 1 vs non-responder cohort 1 vs placebo (pooled)		**x**
14.2.5.13	Figure: Individual NPI total score by KBIT-2 score: Absolute value by responder cohort 2 vs non-responder cohort 2 vs placebo (pooled)		**x**

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.2.5.14	Figure: Individual NPI total score by KBIT-2 score: Absolute value by Responder cohort 1 and 2 (pooled) vs non-responder cohort 1 and 2 (pooled) vs placebo		**x**
14.3	**SAFETY AND TOLERABILITY**	**SAF**	
14.3.1	**Extent of exposure**		
14.3.1.1	Extent of exposure		
14.3.1.2	Time between visits and total study duration		
14.3.2	**Adverse events**		
14.3.2.1	Adverse event summary table		
14.3.2.2	TEAEs by system organ class and preferred term		
14.3.2.3	TEAEs by intensity/severity grading		
14.3.2.4	TEAEs by causal relationship		
14.3.2.5	Study-drug related TEAEs (ADRs)		
14.3.2.6	Serious TEAEs (SAEs)		
14.3.2.7	Serious study-drug related TEAEs (serious ADRs)		
14.3.2.8	Injection site reactions		
14.3.2.9	Injection site reactions by intensity		
14.3.2.10	Injection site reactions – onset time and resolution		
14.3.2.11	Figure: Treatment emergent adverse events with an incidence rate >= 10%, horizontal bar chart		
14.3.3	Global assessment of tolerability		
14.3.4	Physical examination: Body height, weight, BMI		
14.3.5	Physical examination: Body system		
14.3.6	**Vital signs**		
14.3.6.1	Vital signs: Descriptive measures for absolute values		
14.3.6.2	Vital signs: Descriptive measures for change from baseline values		
14.3.7	Neurological examination		
14.3.8	**Suicidal ideation/ behavior**		
14.3.8.1	Suicidal ideation/behavior: General questions		
14.3.8.2	Columbian-suicide severity rating scale (C-SSRS)		

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.3.9	**12-lead ECG**		
14.3.9.1	12-lead ECG: Descriptive analysis of ECG parameters		
14.3.9.2	12-lead ECG: Analysis of tendency		
14.3.9.3	12-lead ECG: Categorical analysis by visit		
14.3.9.4	12-lead ECG: Categorical analysis: Maximum QTc prolongation		
14.3.10	**Clinical laboratory**		
14.3.10.1	**Screening tests**		
14.3.10.1.1	Screening tests – Continuous outcome parameters		
14.3.10.1.2	Screening tests - Categorical parameters		
14.3.10.2	**Central laboratory: Hematology**		
14.3.10.2.1	Central laboratory: Hematology – Descriptive statistics		
14.3.10.2.2	Central laboratory: Hematology – Change from baseline		
14.3.10.3	**Central laboratory: Clinical chemistry**		
14.3.10.3.1	Central laboratory: Clinical chemistry – Descriptive statistics		
14.3.10.3.2	Central laboratory: Clinical chemistry – Change from baseline		
14.3.10.4	**Central laboratory: Coagulation**		
14.3.10.4.1	Central laboratory: Coagulation – Descriptive statistics		
14.3.10.4.2	Central laboratory: Coagulation – Change from baseline		
14.3.10.5	**Central laboratory: Biochemistry evaluation of urine**		
14.3.10.5.1	Central laboratory: Biochemistry evaluation of urine – Descriptive statistics		
14.3.10.5.2	Central laboratory: Biochemistry evaluation of urine - Categorical parameters		
14.3.10.5.3	Central laboratory: Biochemistry evaluation of urine – Change from baseline		
14.3.10.6	**Central laboratory: Immunology – Immunoglobulin G**		
14.3.10.6.1	Central laboratory: Immunology – Immunoglobulin G -Descriptive statistics		
14.3.10.6.2	Central laboratory: Immunology – Immunoglobulin G - Change from baseline		
14.3.10.7	**ApoE genotyping**		
14.3.10.7.1	Figures: Biomarkers in plasma (Aβ1-42, Aβ1-40, total tau) by ApoE4 carriers versus non-carriers: Median absolute value		x

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.3.10.7.2	Figures: Biomarkers in serum (NfL) by ApoE4 carriers versus non-carriers: Median absolute value		x
14.3.10.7.3	Figures: Biomarkers in CSF (Aβ1-38, Aβ1-42, total tau, phospho-tau, NfL and Neurogranin) by ApoE4 carriers versus non-carriers: Median absolute value		x
14.3.10.7.4	Figures: CANTAB (MOT, RTI or PAL) results by ApoE4 carriers versus non-carriers: Mean absolute value		x
14.3.10.7.5	Figures: total BPT score by ApoE4 carriers versus non-carriers: Mean absolute value		x
14.3.10.7.6	Figures: VABS-II transformed domain standard scores 1.-3. by ApoE4 carriers versus non-carriers: Mean absolute value		x
14.3.10.7.7	Figures: NPI total score and the caregiver distress score (continuous) by ApoE4 carriers versus non-carriers: Mean absolute value		x
14.3.10.7.8	Figures: Volumetric MRI percent change atrophy parameters (by location and laterality) by ApoE4 carriers versus non-carriers: Mean absolute value		x
14.3.10.8	**Inflammatory markers in blood**		
14.3.10.8.1	Inflammatory markers in blood: Descriptive statistics and clinical significance		
14.3.10.8.2	Inflammatory markers in blood: Change from baseline		
14.3.10.9	**MRI imaging**		
14.3.10.10	Previous and concomitant medication		
14.3.10.10.1	Previous medication		
14.3.10.10.2	Concomitant medication		
14.4	**BIOLOGICAL ENDPOINTS**	**mITT, PPS**	
14.4.1	**Primary biological endpoint: Anti-Aβ1-42 IgG titer in serum**		
14.4.1.1	Anti-Aβ1-42 IgG titer in serum: Responders		
14.4.1.2	Anti-Aβ1-42 IgG titer in serum: Descriptive statistics		
14.4.1.3	Anti-Aβ1-42 IgG titer in serum: Change from baseline. percent change from baseline		
14.4.1.4	Anti-Aβ1-42 IgG titer in serum: Descriptive statistics for AUC		
14.4.1.5	**Figures: Anti-Aβ1-42 IgG titer in serum**		
14.4.1.5.1	Figures: Anti-Aβ1-42 IgG titer in serum: Mean absolute value		

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.4.1.5.2	Figures: Anti-Aβ1-42 IgG titer in serum: Geometric mean absolute value		
14.4.1.5.3	Figures: Anti-Aβ1-42 IgG titer in serum: Mean change from baseline		
14.4.1.5.4	Figures: Anti-Aβ1-42 IgG titer in serum: Mean percent change from baseline		
14.4.1.5.5	**Figures: Individual time course of anti-Aβ1-42 IgG titer in serum**		
14.4.1.5.5.1	Figures: Individual anti-Aβ1-42 IgG titer in serum: Absolute value grouped by treatment group		
14.4.1.5.5.2	Figures: Individual anti-Aβ1-42 IgG titer in serum: Absolute value grouped by subject		
14.4.1.5.5.3	Figures: Individual anti-Aβ1-42 IgG titer in serum: Change from baseline		
14.4.1.5.5.4	Figures: Individual anti-Aβ1-42 IgG titer in serum: Percent change from baseline		
14.4.1.5.6	**Figures: Correlation analyses of individual antibody values**		
14.4.1.5.6.1	Figures Individual anti-Aβ1-42 IgG titer versus each biomarkers in plasma (Aβ1-42, Aβ1-40, total tau): Absolute value		
14.4.1.5.6.2	Figures Individual anti-Aβ1-42 IgG titer versus each biomarkers in serum and CSF: Absolute value		
14.4.1.5.6.3	Figures Individual anti-Aβ1-42 IgG titer versus CANTAB (MOT, RTI or PAL): Absolute value		
14.4.1.5.6.4	Figures Individual anti-Aβ1-42 IgG titer versus BPT score: Absolute value		
14.4.1.5.6.5	Figures Individual anti-Aβ1-42 IgG titer versus VABS/II transformed domain standard scores 1.-3: Absolute value		
14.4.1.5.6.6	Figures Individual anti-Aβ1-42 IgG titer against total NPI score and the caregiver distress score (continuous): Absolute value		
14.4.1.5.6.7	Figures Individual anti-Aβ1-42 IgG titer versus volumetric MRI percent change atrophy parameters (by location and laterality): Absolute value		
14.4.1.5.6.8	Figures Individual anti-Aβ1-42 IgG titer grouped by median split age groups: Absolute value		
14.4.1.5.6.9	Figures Individual anti-Aβ1-42 IgG titer versus BMI: Absolute value		
14.4.1.5.7	Figures: Correlation analyses of mean group antibody values		
14.4.1.5.7.1	Figures: Anti-Aβ1-42 IgG titer versus each biomarkers in plasma (Aβ1-42, Aβ1-40, total tau): Mean absolute value		
14.4.1.5.7.2	Figures Anti-Aβ1-42 IgG titer versus each biomarkers in serum (NfL) and CSF (Aβ1-38, Aβ1-42, total tau, phospho-tau, NfL and Neurogranin): Mean absolute value		
14.4.2	**Anti-Aβ1-42 IgM titer in serum**		

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.4.2.1	Anti-Aβ1-42 IgM titer in serum: Descriptive statistics		
14.4.2.2	Anti-Aβ1-42 IgM titer in serum: Change from baseline		x
14.4.3	**(Volumetric) MRI**		
14.4.3.1	(Volumetric) MRI: Descriptive statistics		
14.4.3.2	Figures: (Volumetric) MRI: Mean percent change from baseline		
14.4.4	**Blood T-cell activation (IFN-γ and IL-4 release)**		
14.4.4.1	Blood T-cell activation (IFN-γ and IL-4 release): Descriptive statistics		x
14.4.4.2	Blood T-cell activation (IFN-γ and IL-4 release): Change from baseline		x
14.4.4.3	Figures: Blood T-cell activation (IFN-γ and IL-4 release): Absolute values		x
14.4.4.4	Figures: Blood T-cell activation (IFN-γ and IL-4 release): Change from baseline values		x
14.4.4.5	Figures: Blood T-cell activation (IFN-γ and IL-4 release): Percent change from baseline values		x
14.4.5	**Biomarkers in plasma, in serum and in CSF**		
14.4.5.1	Biomarkers in plasma: Descriptive statistics		
14.4.5.2	Biomarkers in plasma: Change from baseline		
14.4.5.3	**Figures: Biomarkers in plasma**		
14.4.5.3.1	Figures: Biomarkers in plasma: box plots		
14.4.5.3.2	Figures: Individual biomarkers in plasma: Absolute value		
14.4.5.3.3	Figures: Individual biomarkers in plasma: Change from baseline		
14.4.5.3.4	Figures: Individual biomarkers in plasma: Percent change from baseline		
14.4.5.3.5	Figures: Biomarkers in plasma: Mean absolute value		
14.4.5.3.6	Figures: Biomarkers in plasma: Mean change from baseline		
14.4.5.3.7	Figures: Biomarkers in plasma: Mean percent change from baseline		
14.4.5.4	Biomarkers in serum: Descriptive statistics		
14.4.5.5	Biomarkers in serum: Change from baseline		
14.4.5.6	**Figures: Biomarkers in serum**		
14.4.5.6.1	Figures: Biomarkers in serum: box plots		
14.4.5.6.2	Figures: Individual biomarkers in serum: Absolute value		
14.4.5.6.3	Figures: Individual biomarkers in plasma: Change from baseline		

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.4.5.6.4	Figures: Individual biomarkers in plasma: Percent change from baseline		
14.4.5.6.5	Figures: Biomarkers in serum: Mean absolute value		
14.4.5.6.6	Figures: Biomarkers in serum: Mean change from baseline		
14.4.5.6.7	Figures: Biomarkers in serum: Mean percent change from baseline		
14.4.5.7	Biomarkers in CSF: Descriptive statistics		
14.4.5.8	Biomarkers in CSF: Change from baseline		
14.4.5.9	**Figures: Biomarkers in CSF**		
14.4.5.9.1	Figures: Biomarkers in CSF: box plots		
14.4.5.9.2	Figures: Individual biomarkers in CSF: Absolute value		
14.4.5.9.3	Figures: Individual biomarkers in CSF: Change from baseline		
14.4.5.9.4	Figures: Individual biomarkers in CSF: Percent change from baseline		
14.4.5.9.5	Figures: Biomarkers in CSF: Mean absolute value		
14.4.5.9.6	Figures: Biomarkers in CSF: Mean change from baseline		
14.4.5.9.7	Figures: Biomarkers in CSF: Mean percent change from baseline		
14.4.6	**Angiogenic proteins and vascular injury markers in plasma**		
14.4.6.1	Angiogenic proteins and vascular injury markers in plasma: Descriptive statistics		x
14.4.6.2	Angiogenic proteins and vascular injury markers in plasma: Change from baseline		x
14.4.6.3	Figures: Angiogenic proteins and vascular injury markers in plasma: Mean absolute value		x
14.4.6.4	Figures: Angiogenic proteins and vascular injury markers in plasma: Mean change from baseline		x
14.4.6.5	Figures: Angiogenic proteins and vascular injury markers in plasma: Mean percent change from baseline		x
14.4.6.6	Figures: Individual angiogenic proteins and vascular injury markers in plasma: Absolute value		x
14.4.6.7	Figures: Individual angiogenic proteins and vascular injury markers in plasma: Change from baseline		x
14.4.6.8	Figures: Individual angiogenic proteins and vascular injury markers in plasma: Percent change from baseline		x
14.4.7	**Inflammatory cytokines in serum**		**x**

Table/Figure Number	Table/Figure Description	Analysis Set	Additional TLF – delivered separately after initial set of TLFs
14.4.7.1	Inflammatory cytokines in serum: Descriptive statistics		x
14.4.7.2	Inflammatory cytokines in serum: Change from baseline		x
14.4.7.3	Figures: Inflammatory cytokines in serum: Mean absolute value		x
14.4.7.3	Figures: Inflammatory cytokines in serum: Mean change from baseline		x
14.4.7.3	Figures: Inflammatory cytokines in serum: Mean percent change from baseline		x
14.4.7.4	Figures: Individual inflammatory cytokines in serum: Absolute value		x
14.4.7.5	Figures: Individual inflammatory cytokines in serum: Change from baseline		x
14.4.7.6	Figures: Individual inflammatory cytokines in serum: Percent change from baseline		x

* Same content as for regular DSMB meeting

16.3.2 List of data listings for final analysis

Listing Number	Listing Description
16.2	**SUBJECT DATA LISTINGS**
16.2.1	**Discontinued subjects**
16.2.1.1	Study closure form
16.2.2	**Protocol deviations and eligibility**
16.2.2.1	Protocol deviations
16.2.2.2	Eligibility, inclusion/ exclusion criteria
16.2.2.3	Informed consent
16.2.3	**Subjects excluded from the efficacy analysis**
16.2.3.1	Subjects excluded from the efficacy analysis
16.2.3.2	Subject assignment to the analysis populations
16.2.4	**Demographic data**
16.2.4.1	Demographics
16.2.4.2	Child bearing potential
16.2.4.3	Kaufmann brief intelligence test (KBIT-2)
16.2.4.4	Medical history
16.2.5	**Compliance and /or drug concentration data**
16.2.5.1	IMP administration (CRF entries)
16.2.5.2	IMP administration (derived data)
16.2.5.3	Visit dates, time between visits, study duration
16.2.5.3.1	Visit dates: Screening visit - visit 12
16.2.5.3.2	Visit dates: Visit 13 - visit 21
16.2.5.3.3	Visit dates: Unscheduled visits
16.2.5.3.4	Time between visits: Screening visit - visit 10
16.2.5.3.5	Time between visits: Visit 10 - visit 19
16.2.5.3.6	Time between visits: Visit 19 - visit 21, study duration
16.2.6	**Individual efficacy response data**
16.2.6.1	Clinical global impression of change (CGIC)
16.2.6.2	Cambridge neuropsychological test automated battery (CANTAB) – Raw values and change from baseline
16.2.6.3	Repeatable battery for the assessment of neuropsychological status (RBANS)
16.2.6.4	Brief praxis test (BPT) – Questions and change from baseline
16.2.6.5	Vineland-II adaptive behavior scale (VABS-II) – Raw values and v-scale scores

Listing Number	Listing Description
16.2.6.6	Vineland-II adaptive behavior scale (VABS-II) – transformed, absolute and change from baseline domain standard score
16.2.6.7	Neuropsychiatric inventory (NPI): Subdomains – frequency, severity and frequency x severity
16.2.6.8	Neuropsychiatric inventory (NPI): Absolute and change from baseline Caregiver distress score
16.2.6.9	Neuropsychiatric inventory (NPI): Absolute and change from baseline total NPI score
16.2.7	**Adverse event listings**
16.2.7.1	Adverse events – CRF entries
16.2.7.2	Adverse events – MedDRA coding
16.2.7.3	Listings of deaths and serious adverse events
16.2.7.4	Adverse events – injection site reaction details
16.2.8	**Listing of individual laboratory measurements by subjects**
16.2.8.1	Clinical laboratory
16.2.8.1.1	Screening tests
16.2.8.1.2	Clinical laboratory: Hematology
16.2.8.1.3	Clinical laboratory: Hematology – abnormal subject data listing
16.2.8.1.4	Clinical laboratory: Clinical chemistry
16.2.8.1.5	Clinical laboratory: Clinical chemistry – abnormal subject data listing
16.2.8.1.6	Clinical laboratory: Coagulation
16.2.8.1.7	Clinical laboratory: Biochemistry evaluation of urine
16.2.8.1.8	Clinical laboratory: Biochemistry evaluation of urine – abnormal subject data listing
16.2.8.1.9	Clinical laboratory: Immunoglobulin G
16.2.8.1.10	Clinical laboratory/inflammatory parameters in blood: CRP and ESR
16.2.8.1.11	Clinical laboratory/inflammatory parameters in blood: CRP and ESR – abnormal subject data listing
16.2.8.1.12	Clinical laboratory: Urine and blood pregnancy test
16.2.8.1.13	Clinical laboratory: ApoE
16.2.8.3	**Biological outcome data**
16.2.8.3.1	Anti-Aβ1-42 Ig titer in serum: Raw values, change from pre-treatment and presence of antibody
16.2.8.3.2	Anti-Aβ1-42 Ig titer in serum: AUC
16.2.8.4	Blood T-cell activation (IFN-γ and IL-4 release by T-cells)
16.2.8.5	Biomarkers in plasma and serum
16.2.8.6	Biomarkers in CSF
16.2.8.7	Angiogenic proteins and vascular injury markers in plasma
16.2.8.8	Inflammatory cytokines in serum
16.2.8.9	Inflammatory parameters in CSF

Listing Number	Listing Description
16.2.9	**Further safety evaluations**
16.2.9.1	Global assessment of tolerability
16.2.9.2	**Physical examination and vital signs**
16.2.9.2.1	Physical examination: Body height, weight and BMI
16.2.9.2.2	Physical examination: Body system evaluation
16.2.9.2.3	Vital signs (blood pressure, heart rate, body temperature and respiratory rate) – pre dose
16.2.9.2.4	Vital signs (blood pressure, heart rate, body temperature and respiratory rate) - at/after administration of study medication
16.2.9.3	Neurological examination
16.2.9.4	**Suicidal ideation/ behavior**
16.2.9.4.1	Suicidal ideation/ behavior: General questions
16.2.9.4.2	Columbian-suicide severity rating scale (C-SSRS)
16.2.9.5	**12-lead ECG**
16.2.9.5.1	12-lead ECG: ECG parameters and QTcF, QTcB
16.2.9.5.2	12-lead ECG: Categorical values of QTcF, QTcB and maximum prolongation
16.2.9.6	**Previous and concomitant medication**
16.2.9.6.1	Previous and concomitant medication - details
16.2.9.6.2	Previous and concomitant medication – WHO-DDE coding
16.2.9.7	**MRI/PET imaging**
16.2.9.7.1	Safety: MRI – CRF data
16.2.9.7.2	Safety: MRI – external data
16.2.9.7.3	Biological endpoint: Volumetric MRI
16.2.9.7.4	PET imaging
16.2.10	General comments

* Same content as for regular DSMB meeting

16.4 Appendix D: Table Layouts

Mocks can be found in a separate document.