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GRIFOLS

The attached Analysis Plan has been prepared by:

[redacted]

01 Aug 2018
Date

Principal Statistician
[redacted]

The attached Analysis Plan has been reviewed and approved by:

[redacted]

03 Aug 2018
Date

Director, Statistics
[redacted]

[redacted]

02 Aug. 2018
Date

Medical & Technical Director
Instituto Grifols S.A.

[redacted]

2 Aug 2018.
Date

Program Director
Instituto Grifols S.A.

[redacted]

CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable. This is version 1.0 of the SAP.

2 INTRODUCTION

Note: in this document any text taken directly from the protocol is *italicized*. This SAP described the analysis that is planned for the final analysis of the study data.

2.1 STUDY DESIGN

A clinical trial comprised of 364 subjects with probable mild to moderate AD will be conducted primarily to determine whether short-term followed by long-term, low-volume plasma exchange with human albumin combined with IVIG is able to modify patient's cognitive, functional, behavioral and global domains. There will be 3 treatment groups and one control group. The subjects will be randomized in a 1:1:1:1 proportion.

After screening and randomization, treatment groups will proceed as follows:

- *One month and a half (6 weeks) of intensive treatment with one plasma exchange per week. All 3 treatment groups are the same during the intensive treatment phase.*
- *Two of the three groups will follow 12 months of maintenance treatment with one low-volume plasma exchange every month combined with IVIG every 4 months administered at the end of the corresponding plasmapheresis instead of albumin (that is, 9 plasmaphereses with Albumin replacement and 3 plasmaphereses with IVIG replacement). During this year, treatment-group patients will follow one of the two different pre-allocated treatment arms: 1) with the doses of albumin and IVIG needed to replace those removed during the plasmapheresis, 2) with half of the doses of albumin and IVIG.*
- *One of the three groups will follow the same schedule as the above two groups but with half of the doses of albumin alone (without IVIG), that is, 12 plasmaphereses with half-dose albumin alone.*

Patients in the control group will undergo sham procedures mimicking plasmaphereses but with neither fluid exchange nor albumin or IVIG administrations.

There are also a total of 18 patients who completed the study under protocol Version 1.0. The treatment under Version 1.0 of the protocol was not blinded but the treatment schema was similar to protocol Version 2.0 or later versions. Because there was no sham treatment in Version 1, the randomization date will be used as study start date for the

control patients. However, according to Version 1.0, laboratory values have only been assessed at Baseline, the intermediate visit, LVPE4, LVPE7, LVPE10, and the final Visit. The data from all protocols will be combined for the final analysis wherever possible. These study patients treated under protocol Version 1.0 will be combined to the treatment groups from protocol Version 2.0 or later versions of the protocol as follows:

- Treatment arm A: (100% albumin+Flebo V1.0) + (100% albumin+Flebo V2.0)
- Treatment arm B: (1/2 albumin+Flebo V1.0) + (1/3 albumin+Flebo V1.0) + (1/2 albumin+Flebo V2.0)
- Treatment arm C: (1/2 albumin V2.0)
- Treatment arm D (no treatment): (Control V1.0) + (Sham V2.0)

where V2.0 is protocol Version 2.0 or later versions.

A sample size of 312 subjects (78 per each of the 4 groups) will make it possible to detect with nearly 92% power for the first of the co-primary efficacy variables (the changes from baseline of the ADAS Cog scores) a difference in the mean of 3 points between any of the treatment groups and the control group, assuming the common standard deviation (SD) to be 5.55 (according to the data obtained in the phase II study), with a level of significance of 5%. This same sample size provides over 98% power for second of the co-primary end point variables (the changes from baseline of the ADCS-ADL scores) a difference in the mean of 6.69 points between any of the treatment groups and the control group, assuming the common standard deviation (SD) to be 10.0 (according to the data obtained in the phase II study), with a level of significance of 5%.

*The study will have joint power for these co-primary end points of at least 90% (0.92*0.98 = 0.90). The calculation makes the conservative assumption that these end points are independent. Since these end points are positively correlated 90% should serve as a lower bound on power.*

Assuming a global dropout rate of approximately 15%, the study would have to enroll 364 subjects to obtain 312 subjects for evaluation.

2.2 STUDY OBJECTIVES

Primary objective:
To evaluate the changes in the cognitive, functional, behavioral and global domains based on the different applicable psychometric batteries and scales.

Secondary objectives:

- *To determine the changes in the concentration of beta-amyloid peptide in plasma and cerebrospinal fluid (CSF) in the treatment group of patients with Alzheimer's disease (AD).*
- *To evaluate the structural changes in volume of the hippocampus, posterior cingulate area, and other associated areas based on neuroimaging studies with Magnetic Resonance Imaging (MRI) (variations versus baseline).*
- *To determine functional brain functional changes through FDG-PET (fluordeoxyglucose-PET).*
- *To determine whether plasma exchange with human albumin combined with intravenous immunoglobulin (IVIG) is safe, taking into account the following factors:*
    - *Type, severity and frequency of adverse reactions during and after the procedure and infusions.*
    - *Changes in vital signs and clinically relevant changes, according to the laboratory test findings. –*
    - *Control of episodes of cerebrovascular accidents with MRI.*

3 INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Unblinding of the study data and final analysis will be performed after the study database has been declared clean and has been locked.

4 HYPOTHESES AND DECISION RULES

4.1 STATISTICAL HYPOTHESES

The null hypothesis for each test is that drug response is equal to placebo response, and the two-sided alternative is that drug response is not equal to placebo response.

4.2 STATISTICAL DECISION RULES

The statistical tests will be performed with a 5% significance level and will be two-sided. In addition to the tests, two-sided 95% confidence intervals (95% CI) will be reported.

Because the end points are co-primaries, both must be statistically significant for the study to provide evidence of efficacy. Therefore, no multiplicity adjustment is needed to adjust for the co-primary end points. However, to account for the three dose group comparisons to placebo and to maintain the overall significance level of 0.05, adjustment for α will be made for multiple dose groups according to the Hochberg[1] procedure. The

Hochberg procedure will be implemented as follows: For each end point, the three dose group comparisons versus placebo will be ordered according to the p-value from the largest to the smallest. If the largest p-value is < 0.05 then all comparisons to placebo will be declared significant. Otherwise, if the second largest p-value is < 0.025 (0.05/2) then this dose and all doses with smaller p-values will be declared significant. Otherwise, if the smallest p-value is < 0.0167 (0.05/3) then this dose will be declared significant. Otherwise, no dose is considered significantly different from placebo. This procedure has been demonstrated to control the overall Type I error at 0.05. Both co-primary end points must be significant at a given dose to provide evidence of efficacy for that dose.

Specifically, the null hypothesis for all inferential analyses, including the primary end points, is that all three treatment groups are equal to placebo. Specific doses will be considered different from placebo if statistically significant following the Hochberg procedure described above. The study is considered positive if at least one dose group differs from placebo in both of the co-primary analyses. Subsequently, secondary end points are considered positive if at least one dose group differs from placebo.

A supportive analysis will be performed in per protocol analysis set for each of the co-primary efficacy end points applying the same respective methodologies, but without adjusting for Type I error.

Secondary end points are also controlled for the three dose comparisons by the method of Hochberg, but there is no formal control for multiple secondary end points; each is tested at overall significance level of 0.05. Interpretation will be based on the weight of the evidence and the totality of the data.

5 ANALYSIS SETS

5.1 FULL ANALYSIS SET (FAS)

All subjects included in the study and subjected to at least one plasma exchange session (i.e., randomized and treated) during the intensive treatment phase (the six first weeks of treatment) will form part of the efficacy population.

Control group subjects will also be included (without the plasma exchange) if they attended at least 1 of the 6 intensive treatment phase visits. For the control group from protocol version 1, patients will be included in the FAS if they have at least the intermediate visit performed.

5.2 PER PROTOCOL ANALYSIS SET (PP)

A second efficacy analysis will also be carried out (per protocol analysis) with the patients who complete the treatment without major breaches in the study protocol.

5.3 SAFETY ANALYSIS SET

All patients included in the study and subjected to at least one plasma exchange session will form part of the safety population.

Control group subjects will also be included (without the plasma exchange) if they attended at least 1 of the 6 intensive treatment phase visits. For the control group from protocol version 1, patients will be included in the safety population if they have at least the intermediate visit performed.

5.4 TREATMENT MISALLOCATIONS

For subjects with errors in treatment allocation, they will be reported for efficacy and safety analyses as follows:

If a subject was:

- Randomized but not treated (treatment is defined as attending post baseline study visits), then they are by definition excluded from the efficacy and safety analyses as actual treatment is missing.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing, but will be reported under the treatment they actually received for all safety analyses.
- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses, but will be reported under the treatment they actually received for all safety analyses.

5.5 PROTOCOL DEVIATIONS

All protocol deviations will be determined and documented prior to final analysis.

The following describes any protocol deviations that relate to the statistical analyses or populations:

5.5.1 Deviations assessed prior to randomization

Deviations prior to the randomization are mainly deviations from the inclusion/exclusion criteria. Deviations from the inclusion/exclusion criteria will be summarized by a frequency table.

5.5.2 Deviations assessed post-randomization

Deviations post-randomization are mainly the following:

- Missing or inappropriate timing of the efficacy or safety assessments
- Deviation from the treatment scheme, e.g. incorrect timing, incorrect dose, or incorrect treatment.
- Application of prohibited concomitant medication.

Deviations from the protocol will be listed and categorized as minor or major protocol deviations prior to database lock.

6 STUDY POPULATION SUMMARY

The set of FAS patients set will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and overall unless otherwise noted.The 3 combined active treatment groups will also be presented for the patient disposition, demographics and the medical history.

6.1 PATIENT DISPOSITION

Patients in the FAS analysis set who completed the study and patients who withdraw from the study will be summarized using descriptive statistics. Patients who withdrew from the study will also be summarized using descriptive statistics by reason for withdrawal. The denominator for calculating the percentages will be the set of FAS patients.

Patients enrolled (defined as patients who signed the Informed Consent Form) but not randomized and reason for not being randomized will also be summarized by a frequency table. Also patients randomized but not treated and reason for not being treated will be summarized by a frequency table.

6.2 DEMOGRAPHICS

Demographics characteristics including age, sex, height, weight and calculated body mass index (BMI), will be tabulated and will also include age presented categorically. Missing categories will be presented if necessary.

6.3 MEDICAL HISTORY

Medical history including relevant medical/surgical history, medical history of Alzheimer's disease, and Mini-Mental Status Examination (MMSE) will be summarized using descriptive statistics.

6.4 PRIOR MEDICATIONS

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the first day of study drug treatment. Medication which will be initiated prior to the first day of study treatment and continued after the first day of study drug will counted as both, prior and concomitant medication.

6.5 ELECTROCARDIOGRAM

Electrocardiogram findings (normal, abnormal, and missing) at baseline will be summarized using descriptive statistics.

6.6 PHYSICAL EXAMINATION

Patients with a physical examination, patients with at least 1 abnormal finding, and abnormal findings for each category will be summarized at baseline using descriptive statistics.

7 END POINTS AND COVARIATES

Baseline is defined as the last assessment prior to study drug administration (first full plasma exchange or sham treatment in the control group).

Most summaries will include the 4 treatment groups and cover the entire study period (including both the intensive and maintenance phases), but some analyses (particularly safety) may summarize a specific phase. Summary statistics will be provided for the

actual value and for the change from baseline for each point in time a variable is measured. Only available data will be included in these summary statistics, if not otherwise stated, no substitution of missing values will be done. In addition to the analysis at each point in time a variable is measured, for the safety variables and the biomarkers an analysis will also be performed for the last non-missing post-baseline value (end point).

Study days will be numbered relative to the first day of study drug administration. The start of treatment (Day 1) is defined as the date on which a patient receive the first study treatment. Days will be numbered relative to study start (i.e., ..., –2, –1, 1, 2, ...; with day 1 being the first administration of study treatment and day –1 being the day before the first administration of study treatment).

Protocol-defined efficacy assessments will be "slotted" to study visits based on collection date and applying the rules summarized in the following table. The study day range is the time period where assessments can be selected to populate a study visit, e.g. the assessments from study day 92 to study day 228 can be considered as assessments for the LVPE Visit 4 (month 6) visits.

Visit	Target Study Day	Study day range
Screening/Baseline		-∞ to 1
FPE Visit 1 (Week 1)*	1	1
Intermediate visit (Week 7-8)	45	2 to 93
LVPE Visit 4 (Month 6)	141	94 to 184
LVPE Visit 7 (Month 9)	225	185 to 268
LVPE Visit 10 (Month 12)	309	269 to 343
Final Visit	375	344 to ∞
* Reference date for all other visits		

The slotting scheme for the CSF biomarkers will be as follows:

Visit	Target Study Day	Study day range
Screening/Baseline		-∞ to 1
FPE Visit 1 (Week 1)*	1	1
Intermediate visit (Week 7-8)	45	2 to 187
Final Visit	375	188 to ∞
* Reference date for all other visits		

If 2 or more assessments are falling into the range of a study visit, the assessment closest to the targeted study day will be used, if 2 assessments has the same distance to the targeted study day, the assessment after the targeted study day will be used for the summary statistics. The first Full Plasma Exchange Visit (Week1) will be used as reference for the slotting of all efficacy study visits, regardless of whether or not there is any deviation from the protocol regarding to the study treatment.

The biomarkers in plasma are assessed at each plasma exchange visit prior to the exchange (pre-exchange value) and after the plasma exchange (post-exchange value). The biomarkers in plasma will be slotted as follows:

- Baseline value is the last available value prior to treatment initiation (FPE1). If there is no available value prior to the treatment initiation, the pre-treatment value of FPE1 will be used as baseline value.
- No slotting will be applied to the pre- and post-exchange values of FPE1-FPE6, the intermediate visit, and LVPE1-LVPE12.
- If LVPE12 has been performed, the final visit will be analyzed as final visit. Otherwise, the values from the final visit will be slotted to the visit subsequent to the last performed plasma exchange and analyzed as pre-exchange value, e.g. if LVPE4 is the last performed plasma exchange, the value from the final visit will be analyzed as LVPE5 pre-exchange value.

No windowing schemas will be applied to the safety data (e.g. vital signs, laboratory values, etc.). For by-visit summaries, if there are multiple assessments at a post baseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits.

Summaries of clinically significant abnormal values will include all post baseline values (including scheduled, unscheduled, and early termination visits).

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error of the mean, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages.

7.1 EFFICACY END POINT(S)

Primary Efficacy Variables

- *Change from baseline in the cognitive scores as measured by ADAS-Cog (6 measurements: weeks: -3, -2 or -1, and 7-8; months: 6, 9, 12 and 14), and*
- *Change from baseline in the ADCS-ADL 6 measurements: weeks: -3, -2 or -1, and 7-8; months: 6, 9, 12 and 14).*

Secondary Efficacy Variables
Change from baseline in the cognitive, functional and neuropsychiatric scores and overall development as measured by MMSE, NPS battery, NPI, CDR-Sb, ADCS-CGIC, CSDD, C-SSRS. (6 measurements: week: -3, -2 or -1, and 7-8; months: 6, 9, 12 and 14) and QoL-AD, RUD-Lite® (5 measurements: week: -3, -2 or -1; months: 6, 9, 12 and 14).

The set of FAS patients set will be used for all efficacy summaries unless otherwise noted. Summaries will be presented by treatment group unless otherwise noted. The 3 active treatment groups (half albumin, half albumin + IVIG, and full albumin+ IVIG) will also be pooled together and analyzed as combined active treatment group.

Details for each efficacy variable are presented below.

7.1.1 Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog)

The ADAS-Cog Scale is a questionnaire that assesses cognitive performance in 12 different domains. The domains (and the maximum score) are: (word recall (10), commands (5), constructional praxis (5), delayed word-recall task (10), naming objects/figures (5), ideation praxis (5), orientation (8), word recognition (12), remembering test instructions (5), comprehension (5), word finding difficulties (5), and spoken language ability (5). A total score can be derived by summing across all domains (0-80). Within each domain, and for the total, a higher score indicates more cognitive impairment.

The total score will be analyzed as continuous variables, and will be summarized at each time point.

The total ADAS-Cog score at 14 months is the end point for the primary efficacy analysis. The other point in time will be regarded as secondary end points.

7.1.2 Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)

The ADCS-ADL comprises 23 questions covering a wide array of activities of daily living. Many of the activities begin with an assessment of whether that activity is relevant and then, if yes, follow with an assessment of the difficulty. The total score over all activities ranges from 0-78 where a higher score indicates more autonomy (better outcome).

The total score is analyzed as a continuous variable, and will be summarized at each time point.

The total ADCS-ADL score at 14 months is the end point for the primary efficacy analysis. The other point in time will be regarded as secondary end points.

7.1.3 Mini-Mental Status Examination (MMSE)

The MMSE is a brief 30-point questionnaire test that is used to screen for cognitive impairment, where 30 is the best possible score and lower scores indicate cognitive impairment. The MMSE inclusion criterion for this study is between 18 and 26 (both inclusive).

The score is analyzed as a continuous variable, and will be summarized at each time point.

7.1.4 Neuropsychological Specific Battery (NPSB)

The NPSB has a several components which are described separately below.

7.1.4.1 Rey Auditory Verbal Learning (RAVLT)

The RAVLT has 5 scores of immediate recall of a single list (A), followed immediately by recall of words off a different list (B) and then recall of the first list (short-delay). After 30 minutes recall from the first list is assessed (long-delay). The test ends with a test of recognition of the list 'A' words. Each of these tests results in a score between 0 and 15, where higher score indicates better recall. A total score will be calculated as sum of the 5 scores.

The total score and all sub-scores are analyzed as continuous variables, and will be summarized at each time point.

7.1.4.2 NAB Naming Test

The NAB Naming test assesses each subject's ability to name 31 common objects. They are provided with a semantic and then a phonemic cue as needed. The total score ranges from 0 (no objects are named) to 31 (all objects are named).

The total score is analyzed as a continuous variable, and will be summarized at each time point.

7.1.4.3 Symbol Digit Modalities Test (SDMT)

The SDMT assesses each subject's ability to substitute specific numbers for specific symbols after being provided a map. They are asked to map as many symbols to numbers as possible in 90 seconds. The score is the total number of correct numbers and can range from 0 (no correct matches) to 110, where higher scores indicate better performance.

The total score is analyzed as a continuous variable, and will be summarized at each time point.

7.1.4.4 Phonetic and Semantic Verbal Fluency

The phonetic verbal fluency tests assess each subject's ability to come up with lists of words beginning a specific letter. They are asked to come up with words that begin with 'F', 'A' and 'S'. There is no upper limit, but more words indicate better fluency. The total number of words combined over the three lists is calculated for a total fluency score. The semantic verbal fluency test asks subject to name as many animals as possible, and more animals indicate better fluency.

All scores are analyzed as continuous variables, and will be summarized at each time point.

7.1.4.5 Cornell Scale for Depression on Dementia (CSDD)

The CSDD scores the rater's opinion of the subject's level of depression. The scores range from 0 to 38 where higher scores indicate more severe depression.

The total score is analyzed as a continuous variable, and will be summarized at each time point.

7.1.5 Neuropsychiatric Inventory Questions (NPI)

The NPI is a questionnaire covering many neuropsychiatric domains resulting in 2 total scores. The 10 item scoring will be calculated meaning that the two neurovegetative items (sleep and night-time behavior disorders; appetite and eating changes) are not included. The total score for frequency per severity ranges is calculated by multiplying the frequency (1 to 4) by the severity (1 to 3) for each domain (1 to 12) and summing over the 10 domains for a total range of 10 to 120. The total distress score (as rated by the caregiver) sums the distress score (0 to 5) over the 10 domains and ranges from 0 to 50. For both scores, a higher score indicates more impairment.

Both scores are analyzed as continuous variables, and will be summarized at each time point.

7.1.6 Clinical Dementia Rating (CDR-Sb)

The CDR-Sb assesses 6 different domains of dementia: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain (other than personal care) is given a score of 0, 0.5, 1, 2 or 3, where higher scores indicate more severe dementia. The personal care domain is scored as 0, 1, 2 or 3, where higher scores indicate more severe dementia.

Each domain is analyzed as a categorical variable, and will be summarized at each time point.

7.1.7 Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)

The ADCS-CGIC is a single ordinal assessment of the change in each subject's condition compared to baseline. The potential responses are: Marked improvement (1), moderate improvement (2), minimal improvement (3), no change (4), minimal worsening (5), moderate worsening (6), and marked worsening (7).

The ADCS-CGIC will be summarized as a categorical variable at each time point.

7.1.8 Columbia-Suicide Severity Rating Scale (CSSRS)

The CSSRS assesses suicidal ideation, intensity of ideation, and suicidal behavior. For actual attempts, actual lethality and potential lethality are also assessed. Suicidal ideation assesses 5 types of ideation of increasing severity; intensity of ideation measures the intensity of the most severe ideation. Suicidal behavior examines 5 types of behavior. Actual lethality is scored for the most recent, most lethal, and initial actual attempts (range from 0 to 5). If actual lethality is scored as 0 then potential lethality is scored for the most recent, most lethal, and initial actual attempts (range from 0 to 2). For all scales, higher scores indicate more suicidal behavior.

To assess efficacy and changes from baseline the developers recommend analysis of change in suicidal ideation severity (0 to 5). This score is analyzed as a categorical variable, and will be summarized at each time point. The other scores can be analyzed in a similar manner, if indicated.

7.1.9 Quality of Life- Alzheimer's Disease (QoL-AD)

The QoL-AD has both a rating by a family member or caregiver and also a score by the subject. Each score ranges from 13 to 52, where higher scores indicate better quality of life.

Both scores are analyzed as continuous variables, and will be summarized at each time point.

7.1.10 Resource Utilization in Dementia (RUD) Lite Questionnaire

The RUD questionnaire will be analyzed in a descriptive manner. No cost will be calculated. Description of primary caregiver (Age, sex, relationship to patient, Number of children currently living with caregiver, living with patient, number of other caregivers involved, and contribution of primary caregiver among all caregivers) caregiver time, caregiver working status, patient living accommodation, and patient health care resource utilizations (hospitalizations, emergency room visits) and other services (district nurse, home aid/orderly, food delivery, day care, transportation, etc.) will be summarized by descriptive statistics for all assessments where the RUD is applied.

7.1.11 Biomarkers in Plasma and in the CSF
$Aß_{1-40}$ and $Aß_{1-42}$, T-tau, and P-tau in CSF and $Aß_{1-40}$ and $Aß_{1-42}$ in plasma are secondary efficacy parameter. The analysis of these biomarkers is described in Section 7.3.1.

7.2 SAFETY END POINTS

The primary criterion of safety will be the percentage of plasma exchanges (full and low volume exchanges, including the infusion of albumin and IVIG) associated with at least one adverse event that may be related to the study procedure (adverse reactions). In addition, consideration globally will be made of the percentage plasma exchanges (full and low-volume exchanges, including the infusion of albumin and IVIG) involving some adverse event, whether or not related to the procedure.

Vital signs (blood pressure, heart rate, respiration rate, and body temperature) will be recorded before, during and after each plasma exchange session, where required. Evaluation will also be made (where required) of the different laboratory test parameters (blood cell counts, platelet count, prothrombin time (Quick), fibrinogen, total proteins, and calcium).

During the treatment periods (before each plasma exchange) and on the days when there is no replacement, anxiety and restlessness tests will be made based on the Overt

Aggression Scale (OAS) and the Agitated Behavior Scale (ABS), whenever considered opportune.

According to the criterion of the investigator, all the clinically important changes in vital function, laboratory test parameters and neuroimaging findings will be evaluated. Any adverse events occurring following start of treatment will be counted as treatment emergent.

The analysis of tolerability will be based on description of the safety variables according to their nature.

The adverse reactions will be coded according to the adverse events classification of the World Health Organization (WHO) (MedDRA current version), and will be described by a synonym (Preferred Term) and the affected organ / system, the intensity, causality and seriousness.

The safety population will be used for all safety summaries unless otherwise noted. Summaries will be presented by treatment group and overall unless otherwise noted.

7.2.1 Plasma Exchange

The percentage of plasma exchanges (full and low volume exchanges, including the infusion of albumin and IVIG) associated with at least one adverse event that may be related to the study procedure (adverse reactions) will be summarized. Only adverse events with an onset no later than 72 hours after the end of the plasma exchanges (including the infusion of albumin or IVIG) will be considered for this analysis.

Plasma exchanges (full and low volumes exchanges) will also be summarized by the following measures:

- Plasma exchange performed (yes/no)
- Duration of plasma exchange
- Plasma exchange completed (yes/no)

The reasons for not completing the plasma exchanges will be presented in a data listing.

For the full plasma exchanges, also the following measures will be summarized:

- Route to perform full plasma exchange (peripheral / central)
- Number of bottles of albumin used (calculated as numbers of bottles in this batch + all additional bottles).
- Plasma volume exchanged (ml)

- Volume RF infused (ml)

For the low volume plasma exchange, the following parameters will be summarized:

- Target plasma volume
- Target RF volume
- Type of RF used (20% HAS, Other)
- RF infused
- Plasma volume exchanged (calculated as [(PPP $_{\text{post weight}}$ – PPP $_{\text{bag empty}}$) /1.027 g/ml] ml where PPP $_{\text{bag empty}}$ = 41.87g
- Number of bottles Albumin used

For the plasma exchange visits where IVIG are to be infused (1st and 2nd treatment arm, LVPE1, LVPE5, and LVPE9) the following parameters regarding the IVIG dosing will be summarized:

- IVIG infused (yes/no)
- Theoretical IVIG dose (g)
- Infused dose(g)
- Ratio infused dose /theoretical dose
- Number of bottles used

In addition, percentage of plasma exchanges associated with at least one adverse event will also be summarized whether or not related to the procedure and/or study drug.

7.2.2 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be treatment-related (overall and by severity), serious adverse events, and adverse events causing discontinuation from the study.

The incidence of adverse events will be summarized using descriptive statistics by system organ class and preferred term. Patients are counted only once in each system organ class category, and only once in each preferred term category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by severity, patients are counted at the greatest severity. Adverse events missing the flag indicating serious will be excluded from the summary of serious adverse events. In summary tables, AEs will be counted as "Not Related" if the causality with the product was recorded as "Unrelated"; Events will be counted as "Related" if the causality with the product was recorded as "Possibly", or "Probably," or "Unlikely", or if relationship is missing. For the analysis of adverse events, the relationship to the study

procedure will be used as given in the CRF, regardless of whether or not the adverse event has an onset within 72 hours after the end of the last plasma exchange.
The adverse events will be summarized as follows:

- All AEs by SOC and PT
- All AEs by SOC, PT, and severity
- All AEs by SOC, PT, and causality with product
- Related AEs by SOC and PT
- Related AEs by SOC, PT, and severity
- Related AEs by SOC, PT, and relationship (product, procedure, product + procedure)
- Related AEs by SOC, PT, and product (albumin 5%, albumin 20%, Flebogamma DIF 5%)
- All SAEs by SOC and PT
- Related SAEs by SOC and PT
- SAEs with a fatal outcome by SOC and PT

The relationship to the product will be derived from the most recent plasma exchange. For AEs which are on the date of the plasma exchange, it is assumed that the AE is during/post exchange, i.e. the AE will be associated to this PE. For the 3 active treatment groups, the derivation of the product will be as follows:

- For FPE1 to FPE6, the product is albumin 5%
- For LVPE 1, LVPE5, or LVPE 9, for the full albumin + IGIV and the half albumin + IVIG treatment arm, the product will be flebogamma DIF 5%
- For LVPE 1, LVPE5, or LVPE9, for the half albumin treatment arm, the product will be albumin 20%
- For all other LVPEs, the product will be albumin 20%.

The related adverse events and related serious adverse events will also be analyzed based on the number of FPEs, FPEs using central access, FPE using peripheral access, and LVPEs. For this analysis, only AEs with an onset time no longer than 72 hours after the end of the most recent plasma exchange will be considered. If the time of onset is missing, or the end time of the plasma exchange/infusion of albumin or IVIG is missing, the start date of the AE must be within 2 days after the date of the most recent plasma exchange. Adverse events with missing relationship will not be considered in this analysis. Each plasma exchange is counted only once in each SOC and only once in each. Adverse events will also be analyzed by product (albumin 5%, albumin 20%, Flebogamma DIF 5%) based on the number of plasma exchanges. The denominator for this analysis is the number of performed plasma exchanges with the specific products.

Listings for deaths, serious adverse events, adverse events leading to discontinuation, MedDRA dictionary terms for adverse event descriptions, and adverse event preferred terms by patient number will be presented. Adverse events associated with plasma exchanges will also be presented.

7.2.3 Vital Signs

Summary statistics for vital signs will be presented at baseline, each visit, and end point. Actual values and changes from baseline to each visit and end point will be summarized using descriptive statistics. The incidence of clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

Criteria for Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Heart rate	≥120 bpm	Increase of ≥15
	≤50 bpm	Decrease of ≥15
Systolic blood pressure	≥180 mm Hg	Increase of ≥20
	≤90 mm Hg	Decrease of ≥20
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15
	≤50 mm Hg	Decrease of ≥15
Body temperature	≥38.3°C	Change of ≥1.1°C

In order to be identified as clinically significant abnormal, a value would need to meet both conditions: have a value beyond the criterion value and a change of at least the magnitude specified in the change from baseline column.

A listing for clinically significant abnormal vital signs will be presented.

7.2.4 Clinical Laboratory Tests

Summary statistics for biochemistry, proteinogram, hematology, and clotting laboratory tests will be presented at each visit. Actual values and changes from baseline to each visit will be summarized using descriptive statistics. All changes will be changes from the baseline value, there will be no comparisons in the values between the pre- and post FPE values. Maximal shifts from baseline during the FPE and during the LVPE will be summarized using the CTC AE grading system Version 4.03 and patient counts. Shifts for laboratory values which have no CTC AE grade will be based on the normal ranges (below, within, and above the normal range, if applicable).

7.2.5 Physical Examination

Physical examination results will be summarized at each visit using patient counts for each physical examination category.

7.2.6 Concomitant Medications

All concomitant medications (including prescription and over-the-counter medications) taken during the course of the study will be summarized overall. Concomitant medications for AD will be summarized separately and identified by the indication 'Alzheimer Disease' or any other term indicating Alzheimer Disease. Concomitant medications will be coded according to drug class using the World Health Organization (WHO) drug dictionary.

A concomitant medication is any medication that is taken at some time during IG1002 defined as:

- Medications that do not have a stop date before the first dose of study drug in IG1002, or have a start date any time on or after the first dose of study drug.

Concomitant medications will be listed for each subject according to Anatomical Therapeutic Class (ATC) Level III, preferred term and verbatim term. The World Health Organization Drug Reference List (WHODRL) will be used to classify concomitant medications by therapeutic class and preferred term. Concomitant medication usage will be summarized by the number (%) of subjects receiving each medication within each therapeutic class and preferred term. If a subject receives a particular coded medication more than once, the subject will be counted once for that coded medication. If a subject receives more than one coded medication within a therapeutic class, the subject will be counted only once in that therapeutic class.

Concomitant medication for AD will be summarized as follows on the ATC Level III and preferred drug name using counts and percentages:

- All concomitant AD medication taken at any time during the study period
- AD-Medications newly initiated during study period
- AD-Medications discontinued during study period
- AD-Medications interrupted (and re-initiated) during study period, regardless of the dose after the re-initiation
- AD-Medications with a dose increase during the study period

- AD-Medications with a dose reduction during the study period.

Medications missing both start and stop dates, or having a start date prior to the last dose of study medication and missing the stop date, or having a stop date after the start of study drug and missing the start date, will be counted as concomitant.

7.2.7 Overt Aggression Scale (OAS)

The OAS assesses domains: aggressive behavior of the subject and intervention of the clinician. The Total Score Aggressive Behavior ranges from 1-60, where a higher score indicates more aggressive behavior. The Total Score Intervention ranges from 0-27, where a higher score indicates more intervention. Both scores are analyzed as continuous variables, and will be summarized at each time point.

7.2.8 Agitated Behavior Scale (ABS)

The ABS comprises 14 questions that are each rated as absent (score=1), present to a slight degree (2), present to a moderate degree (3), or present to an extreme degree (4). The 14 questions are summed for a total score between 14 and 56, where a higher score indicates more agitated behavior.

The ABS is analyzed as a continuous variable, and will be summarized at each time point.

7.3 OTHER END POINTS

7.3.1 Biomarkers

Levels of $A\beta_{1-40}$, $A\beta_{1-42}$, T-tau, and P-tau, in cerebral spinal fluid will be collected at the randomization visit, the intermediate visit, and at the final visit. Actual values and changes from baseline at each point in time and at end point will be summarized. Furthermore, the change from the intermediate visit until the final visit will be summarized.

$A\beta_{1-40}$, $A\beta_{1-42}$ will be analyzed before and after each plasma exchange. Absolute values and the changes from baseline will be summarized separately for the values before the plasma exchange and after the plasma exchange. The change in the plasma levels (after plasma exchange – before plasma exchange) will be summarized also.

All other biomarkers (β-secretase, γ-secretase, cholesterol, LDL, HDL, VLDL, CRP, rheumatoid factor, IL-1b, IL-6, ferritin, TNF-α, RBC, WBC, lymphocytes, monocytes, neutrophils, eosinophils, glucose, proteins, and albumin) will be analyzed descriptively (absolute values and changes from baseline) as deemed appropriate.

All biomarker data will be analyzed as continuous variables. If the assumption of normality of the changes from baseline is significantly violated (Shapiro-Wilk test <0.05), changes in the biomarkers will be compared between the treatment groups by a Kruskal-Wallis Test. Statistical comparisons for the changes in $A\beta_{1-40}$, $A\beta_{1-42}$ in plasma will only be performed for the values before and after the plasma exchange.
Further exploratory analyses, e.g. correlation between the biomarkers and the cognitive, functional, and neuropsychiatric scores, can be performed as deemed appropriate.

7.3.2 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging data will be analyzed by MMD. The analysis will be specified in a separate SAP document.

7.3.3 Functional Brain Changes through FDG-PET

Functional brain changes through FDG-PET data will be analyzed by MMD. The analysis will be specified in a separate SAP document.

There are no other end points (e.g., PK, PD, Outcomes Research) in the study.

7.4 COVARIATES

For the analysis of the cognitive, functional, and neuropsychiatric scores, the corresponding baseline scores, age, and AD severity will be used as a covariate for each change from baseline model. Disease severity will be defined by the baseline MMSE score as follows:

- MMSE 18 – 21 points
- MMSE 22 – 26 points

An exception is the model for the changes from baseline for the MMSE. This model will only be adjusted for age and the baseline value. Also the models for the subgroups by severity will only be adjusted for age and baseline value.

8 HANDLING OF MISSING VALUES

Subjects with missing values for a given efficacy value at baseline of at the time point analyzed will be treated as missing rather than using imputed values.

The primary analysis will use a statistical methodology shown be robust in the presence of the type of missing data generally found in clinical trials, as described in Section 9.1.1.

Partial dates for adverse events and medications will be imputed to determine appropriate summarization, as follows:

Imputation of start dates (AE, CM) and assessments (LB, E.G., VS)

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

The extent of missing data will be reported to the FDA.

9 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

9.1 STATISTICAL METHODS

9.1.1 Analyses for Continuous Efficacy end points

The primary efficacy end points, changes from baseline of the ADAS-Cog scores and changes from baseline in the ADCS-ADL inventory, will be analyzed over time using a mixed models repeated measures (MMRM) approach[2,3,4]. The MMRM analysis will include fixed-effects factors for month (2, 6, 9, 12, and 14), treatment group, and the month-by-treatment interaction, with adjustment for age, disease severity and baseline ADAS-Cog score or the ADCS-ADL inventory, respectively. The model will include the subject as repeated factor. The covariance structure will be modeled using an "unstructured" (UN) which makes no assumptions about the within-subject variability. Other covariance structures may be considered if the "unstructured" model does not converge, such as AR(1) which assumes that observations close together (e.g., Months 6 and 9) are more highly correlated than observations further apart (e.g., Months 6 and 14). Although month 14 remains the primary time point, the month-by-treatment interaction allows for potential differences in the treatment effect at different time points. Pairwise contrasts will be constructed to compare the each dose group to the placebo group at each month specifically, where the comparison between each dose group and placebo at 14 months is the primary end point. All other comparisons will be regarded as secondary end points. Summary statistics will be provided for the actual values and for the change from baseline.
This MMRM approach can be implemented in SAS by a code similar to the following:

```
ODS output means =means diffs=diffs:
proc mixed data=dataset;
  class subject treatment visit;
  model change  = age ADseverity baseline treatment visit
```

```
                treatment*visit /ddfm=kr noint;
  repeated time /  sub = subject type = un;
  lsmeans treatment*time /slice=time  cl diff OM;
run; quit;
```

The difference from the control group will be obtained from the treatment * time interaction in the LS means statement (diffs dataset).

The analysis of ADAS-Cog change from baseline to month 14, and the ADCS-ADL change from baseline to month 14, will also be analyzed using analysis of covariance (ANCOVA) with treatment group as a fixed effect, and the corresponding baseline value, age and AD severity as a covariate. A similar model will be calculated also for all other point in time where the end points are assessed. This is considered a sensitivity analysis, and comparison of the results to the MMRM results allows for a qualitative assessment of the impact of missing data.

The two co-primary efficacy end points, change from baseline in the ADAS-Cog score and the change from baseline in the ADCS-ADL inventory score will also be analyzed by a random slope model. For this random slope model, time will be used as continuous variable and all observations (scheduled and unscheduled) will be used with the actual study day, rather than the slotted point in time. Subject and time will be used as random factor using an unstructured covariance matrix. Fixed effects in this model are the baseline value, age, AD severity, time, treatment and treatment*time interaction. The treatment effect will be analyzed by evaluating the treatment * time interaction term. This is considered as a second sensitivity analysis.
This random slope model can be implemented in SAS by a code similar to the following:

```
proc mixed data=data;
  class subj;
  model change = baseline age AD severity time trt time*trt/ s;
  random intercept time / type=un subject=subj;
  repeated / type=vc subject=subj;
run;
```

Possible drop-outs during the treatment phase will not only reduce the available sample size for the final analysis, drop-outs might not be at random and can, therefore, introduce bias to the analysis. Patients who experience less benefit from the treatment might have a higher probability to discontinue the treatment compared to patients who have a better outcome. Therefore, the possible impact of the drop-outs needs be evaluated. The baseline values and the changes from baseline in the ADAS-Cog score and the ADCS-ADL inventory score to the intermediate visit, month 6, month 9, and month 12 will be compared descriptively for each treatment group between the patients who completed the study and patients who prematurely dropped out (Patients who did not complete the final assessment at month 14). Possible differences in the response to the treatment and the

patient characteristics between the patients who completed the study and the patients who prematurely dropped out may be further investigated in an explorative manner, if needed.

Due to the added complexity of the MMRM approach, all other efficacy end points with baseline and post-baseline data will analyze change from baseline to that specific time point using analysis of covariance (ANCOVA) with treatment group as a fixed effect, and the corresponding baseline value, age and AD severity as a covariate. Expanded use of MMRM into secondary analyses may be considered if the results for the MMRM and ANCOVA methodologies for the primary analysis are qualitatively different. Summary statistics will be provided for the actual values and for the changes from baseline.

If the assumption of normality is significantly violated, a non-parametric analysis will be used. Specifically, if the Wilk-Shapiro test for normality of the residuals is significant at the 0.01 level, a rank ANCOVA procedure will be applied, as follows. The standardized ranks for both covariate and the response variable will be produced for each stratum. Then linear regression models will be performed on ranked data by stratum to generate the residuals. Finally the stratified mean score test using the value of the residuals as scores will compare the treatment groups using the Cochran-Mantel-Haenszel procedure[5].

This statistical test will be 2-tailed using α=0.05, with adjustment for multiple comparisons as described in Section 4.2.

9.1.2 Analyses for Categorical Efficacy End Points

All ordinally scaled categorical data will be analyzed using CMH test with modified ridit scores which make no assumptions regarding scaling of response level other than that implied by relative ordering. Frequency tables and the CMH test will be applied to the actual value of each visit a variable is measured.

9.1.3 Analyses for Binary End points

Not applicable in current SAP.

9.1.4 Analyses for Biomarkers

Biomarkers with baseline and post-baseline data will be analyzed in the same way as the other efficacy end points using the ANCOVA model with adjustment for age, AD severity, and the baseline value. The biomarkers will also be analyzed by AD severity. The biomarkers assessed by different methods will be analyzed by assessment method.

9.1.5 Analyses for Safety

All analysis of safety will be descriptive statistics. For laboratory values, summary statistics for the actual value and for the change from baseline will be provided. Adverse events will be summarized by frequency counts and percentages.

9.2 STATISTICAL ANALYSES

9.2.1 Primary Analysis

The primary analysis is based on the FAS population and the primary end points of 1) change from baseline in the Total ADAS-Cog change from baseline score and 2) change from baseline in the ADCS-ADL inventory score at month 14 using MMRM as described in Section 9.1.1 above.

To support the interpretation of the primary analysis, an identical analysis as described above, based upon the PP population rather than the FAS, will be conducted.

The co-primary end points ADAS-Cog and ADCS-ADL will also be analyzed by AD severity as defined in Section 7.4. The same primary analysis will be performed as for the entire population with the exception that the MMRM will not be adjusted for AD severity.

9.2.2 Secondary Analyses

All other efficacy analyses are considered secondary. Basic descriptions of the end points can be found in Section 7.1. For a full list of secondary analyses, please see Section 9.2.4.

9.2.3 Safety Analyses

All safety analyses are descriptive with no inferential statistics. Descriptions of the safety end points and their proposed analysis can be found in Section 7.2.

9.2.4 Analysis of Biomarkers

Analysis of biomarkers will be performed as described in Section 9.1.4.

9.2.5 Summary of Efficacy Analyses

End point	Analysis Set	Statistical Method	Model/ Covariates	Missing Data	Interpretation/Comments
Total ADAS-Cog at Month 14	**FAS**	**MMRM**	**Treatment/Week Bsl/Age/AD severity**	**Uses all non-missing data**	**Co-Primary Analysis**
	PP	MMRM	Treatment/Week/Bsl/Age/AD Severity	Uses all non-missing data	Check for robustness of primary analysis
	FAS	ANCOVA	Treatment/Bsl/Age/AD Severity	Excluded	Sensitivity analysis
	FAS	ANCOVA	Treatment/Bsl/Age/AD Severity	LOCF	Check for impact of missing data on standard ANCOVA models.
	FAS	Random Slope Model	Treatment/Time/ Bsl/Age/AD Severity	Uses all non-missing data	Sensitivity analysis
Total ADAS-Cog at Time Points	FAS	ANCOVA	Treatment/Bsl/Age/AD Severity	Excluded	Secondary analysis of investigation of time course of efficacy
Total ADCS-ADL at Month 14	**FAS**	**MMRM**	**Treatment/Week Bsl**/Age/AD Severity	**Uses all non-missing data**	**Co-Primary Analysis**
	PP	MMRM	Treatment/Week/Bsl/Age/AD Severity	Uses all non-missing data	Check for robustness of primary analysis
	FAS	ANCOVA	Treatment/Bsl/Age/AD Severity	Excluded	Sensitivity analysis

	FAS	ANCOVA	Treatment/Bsl	LOCF	Check for impact of missing data on standard ANCOVA models.
	FAS	Random Slope Model	Treatment/Time/ Bsl/Age/AD Severity	Uses all non-missing data	Sensitivity analysis
Total ADCS-ADL at Time Points	FAS	ANCOVA	Treatment/Bsl/Age /AD Severity	Excluded	Secondary analysis of investigation of time course of efficacy
ADAS-Cog domains at Time Points (12 domains)	FAS	ANCOVA	Treatment/Bsl/Age /AD Severity	Excluded	Secondary analysis of ADAS-Cog domains
MMSE at Time Points	FAS	ANCOVA	Treatment/Bsl/Age /AD Severity	Excluded	Secondary analysis of cognitive impairment
Neuropsychological Specific battery (NPSB) with it's components RAVLT (5 scores), NAB naming test (1 score), SDTM (1 score), Phonetic and semantic fluency (2 scores) CSDD (1 score) at Time Points	FAS	ANCOVA	Treatment/Bsl/Age /AD Severity	Excluded	Secondary analysis of cognitive impairment
Neuropsychiatric inventory questions	FAS	ANCOVA	Treatment/Bsl/Age /AD Severity	Excluded	Secondary analysis of cognitive impairment

(NPI) (2 total scores)Time Points					
Clinical Dementia Rating CDR-Sb (6 domains)	FAS	CMH test (values on time point)		Excluded	Secondary analysis of cognitive impairment
ADCS –CGIC (1 score)	FAS	CHM test (values on time point)		Excluded	Secondary analysis of cognitive impairment
C-SSRS, suicidal ideation severity (1 score)	FAS	CHM test (values on time point)	Treatment/Bsl/Age /AD Severity	Excluded	Secondary analysis of cognitive impairment
QoL-AD (2 scores)	FAS	ANCOVA	Treatment/Bsl/Age /AD Severity	Excluded	Secondary analysis of cognitive impairment
RUD lite	FAS	Summary statistics for individual items			Descriptive analysis for resource consumptions.
Biomarkers at Time Points	FAS	ANCOVA	Treatment/Bsl/Age /AD Severity	Excluded	Biomarkers as secondary end points.

10 REFERENCES

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