A Randomized Double-Blinded Placebo-Controlled Exploratory Study of Intravenous Immunoglobulin (NewGam 10%) in Amnestic Mild Cognitive Impairment

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1.0 BACKGROUND

Alzheimer disease (AD), the most common cause of dementia, is a neurodegenerative disorder with the pathological abnormality of beta-amyloid (Aβ) plaques. One promising treatment for AD aims at clearing Aβ plaques through immunotherapy. Patients with amnestic mild cognitive impairment (a-MCI) are a group recognized at being at high risk of progressing to Alzheimer disease. Treatment of a-MCI with immunotherapy with intravenous immunoglobulins (IVIG) could potentially reduce the risk of progression to Alzheimer disease.

Evidence for immunotherapy as a therapy for AD had its beginnings in 1996 when Solomon and colleagues demonstrated in vitro that Aβ monoclonal antibodies disassembled Aβ fibrils. This potential strategy of immunotherapy for AD was further supported by Schenk, et al. [1] who found that Aβ vaccination of mice diminished Aβ plaques.

Immunotherapy research eventually progressed to a phase II trial of active immunization against Aβ-42 in 2001 and initially showed promising results. The group of subjects who successfully developed Aβ antibodies showed not only a significantly slower rate of cognitive decline over one year compared to the placebo group, but also improvement in memory scores which positively correlated with antibody titer [2]. A later neuropathological examination of three AD patients who were actively immunized against Aβ (deaths were not attributed to the immunization) revealed remarkable clearance of cortical Aβ [3]. Unfortunately, 6% of the 298 participants who were immunized developed an aseptic meningoencephalitis and the trial was discontinued [4].

A leading theory regarding the etiology of this postvaccination meningoencephalitis is T-cell mediated inflammation triggered by the Aβ-42 molecule used for active immunization [4]. One strategy to avoid this adverse inflammation is to administer the Aβ antibodies passively such as via IVIG.

Commercial IVIG has been shown to contain antibodies to Aβ [5] [6]. The molecular mechanism of Aβ clearance by IVIG was studied in vitro by Istrin and colleagues [6] who found that the antibodies in IVIG disassembled the fibril plaques by enhancing microglial migration thus leading to the phagocytosis of Aβ.

In an open-label study, Dodel and colleagues [7] found that AD patients treated with IVIG (Octagam® 0.4 g/kg daily x 3 days every 4 weeks for 6 months) demonstrated a mean cognitive improvement of 3.7 points on the ADAS-cog after 6 months of treatment. Dodel et al. [7] also found that Aβ levels in the CSF decreased by 30% whereas serum Aβ levels increased, thus supporting amyloid clearance theories. There were no serious adverse events associated with IVIG in this study.

Relkin et al. [8] completed an 18-month open-label study of IVIG (Gammagard) for mild AD where subjects were randomized to four consecutive dosing periods: 1) 0.4 g/kg every 2 weeks, 2) 0.4 g/kg/week, 3) 1 g/kg every 2 weeks, and 4) 2 g/kg every 4 weeks for 6 months followed by a 3-month washout. All patients were then treated with 1g/kg every 2 weeks starting in months 10 through 12, then 0.4 g/kg every 2 weeks starting in months 13-18. The results showed a dose-dependent increase in serum Aβ suggesting amyloid clearance. A mean improvement of 2.5 points on the MMSE after 6 months (and mean improvement of 0.5 points at 18 months) was observed; this is contrasted to the expected 1.5 point decline per 6 months with AD. Higher doses of IVIG did not lead to higher cognitive scores and, in fact, the group treated

with the lowest dose of 0.4 g/kg per week maintained the highest MMSE scores. There were no serious adverse events during this study.

In a Phase II trial of IVIG (Gammagard 10%) in mild to moderate Alzheimer disease, Relkin et al [9] studied IVIG at doses ranging from 0.2 to 0.8 g/kg every two to four weeks over 18 months. The study demonstrated significantly decreased cognitive decline on the ADAS-cog as well as significantly decreased brain atrophy in subjects receiving early IVIG compared to the delayed treatment arm (placebo for 6 months then IVIG). On MRI, the annual ventricular enlargement rate was 6.7% for those treated with IVIG compared to 12.3% for those previously taking placebo; the rate of atrophy was lowest with the IVIG dose of 0.4 g/kg every 2 weeks. There were no serious adverse events during this study.

There are two ongoing phase III trials of IVIG 10% (Octagam and Gammagard) for mild to moderate AD.

In July 2009, Fillit et al [10] published a retrospective analysis of the risk of AD and related disorders in people ≥ 65 with a prior history of one or more IVIG treatments for indications other than AD. Cases were matched to controls on age, gender, and risk factors for AD and related disorders. This study analyzed an approximate 4-year period and demonstrated that previous treatment with IVIG was associated with a 42% lower risk of developing AD and related disorders.

The potential protective effect of IVIG against AD could best be utilized in persons identified to be at greatest risk for developing AD prior to the development of advanced disease and neuropathology. Persons with a-MCI have been identified a group at high risk of progressing to AD with a conversion rate of approximately 15% per year. [11, 12] Vermuri used data from the Alzheimer Disease Neuroimaging Initiative including CDR-SB and MMSE to assess disease progression (while investigating potential biomarkers, MRI and CSF) of AD and demonstrated that 60 of the 192 subjects with a-MCI converted to AD over 1.5 years; i.e., annual conversion rate from a-MCI to AD of 20.8% [13].

This study will investigate treating persons with a-MCI with IVIG (NewGam 10%) 0.4g/kg every 14 days over the course of three months with the intent of showing differences in brain MRI volume, cognition, and conversion to AD when compared with placebo after 24 months. We chose this dose of IVIG based on recent evidence from Relkin [8] who showed that this may be an optimal IVIG dose for reduction of brain atrophy in patients with AD. Furthermore, Fillet [10] demonstrated a lower risk of AD in patients who had received only one treatment of IVIG.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary objective

This randomized double-blinded study will evaluate the efficacy of intravenous immunoglobulin (NewGam 10%) in patients with a-MCI over 24 months after the first infusion.

2.2 Secondary objective

Additionally, this randomized double-blinded study will evaluate the efficacy of intravenous immunoglobulin (NewGam 10%) in patients with a-MCI over 36 months, 48 months, and 60 months after the first infusion.

2.3 Primary endpoint

- Change in ventricular volumetric as measured by MRI at baseline, 24 months, 36 months, 48 months, and 60 months following the first infusion of either 0.4 g/kg NewGam or 0.9% saline solution (placebo) every 14 days x 5.

2.4 Secondary endpoints

- Conversion from a-MCI to AD as measured by NINCDS-ADRDA, National Institute on Aging (NIA) criteria for diagnosis of Alzheimer Disease, [14] and Clinical Dementia Rating (CDR)
- Change in ventricular volume as measured by MRI at baseline, 12 months, 24 months, 36 months, 48 months, and 60 months following infusion of either 0.4 g/kg NewGam or 0.9% saline solution (placebo) every 14 days x 5 in patients with positive CSF Aβ1-42/CSF P-Tau_{181P} Alzheimer signature
- Change in cognitive performance between baseline and 4, 8, 12, 16, 20, 24, 36, 48, and 60 months after the first infusion as measured by:Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog)
- Mini Mental State Exam (MMSE)
- Clinical Dementia Rating (CDR) and Sum of Boxes (CDR-SB)

3.0 STUDY PLAN

3.1 Study design

This is a single center, randomized, double blind, placebo controlled, parallel-group, out-patient study in male and female subjects aged 50 to 84 years with amnestic-mild cognitive impairment. Subjects will be randomized to receive either an infusion of IVIG at 0.4 g/kg or 0.9% saline solution (placebo) every 14 days for two months for a total of five infusions.

Fifty subjects will be enrolled and randomized in a 1:1 IVIG 2.0 g/kg: placebo ratio. Twenty-five subjects will receive IVIG and 25 subjects will receive placebo.

3.2 Subject population

Subject population will consist of male and female subjects diagnosed with amnestic-mild cognitive impairment

3.3 Estimated study duration

The duration of each study subject is approximately 24 months, including one screening visit over a period of approximately 28 days, 5 days of infusions over a 2-month period of time, and follow-up visits at 4, 8, 12, 16, 20, and 24 months after the first infusion. Subjects will be given the option to continue study follow-up visits at 36, 48, and 60 months after the first infusion.

4.0 SUBJECT SELECTION

Following are the eligibility criteria designed to select subjects who are considered appropriate for this protocol.

4.1 Inclusion criteria

1. Signed and dated written informed consent obtained from the subject in accordance with the local regulations. The subject's collaborative informant must also consent to participate in the study.
2. Age from 50 to <85 years.

3. Diagnosis of Mild Cognitive Impairment, Amnestic type (single or multi domain) according to Petersen criteria (Appendix B), NIA diagnostic guidelines, [15] and supported by a CDR score of 0.5.
4. Mini-Mental State Examination (MMSE) score of 24-30, inclusive.
5. Rosen Modified Hachinski Ischemic score ≤4.
6. Willing to consent to ApoE testing and agree to disclose ApoE4 status. Previous ApoE testing will be accepted.
7. Receiving stable doses of medication(s) for the treatment of non-excluded medical condition(s) for at least 30 days prior to screening.
8. Agree to refrain from taking any medication, vitamin, or herbal supplement indicated for a-MCI or AD or considered to enhance cognition unless approved by the investigator for the duration of the study.
9. Ability to attend all clinical visits and have an informant capable of accompanying the subject on specific clinic visits for two years or the duration of the study.
10. The subject's collaborative informant (support person) must be someone who has known the subject for at least 4 years; agrees to have at least 2 separate communications with the study participant per month for the duration of the study (one of these communications must be in person); and attends and completes the CDR interview at 8 study visits along with the subject.
11. Fluency in English and evidence of adequate premorbid intellectual functioning.
12. Adequate manual dexterity, visual, and auditory abilities to perform all aspects of the cognitive and functional assessments.
13. Venous access suitable for repeated infusion and phlebotomy.
14. In the opinion of the investigator, the subject and informant will be compliant and have a high probability of completing the study, including all scheduled evaluations and required tests.

4.2 Exclusion criteria

ANY one of the following will exclude a subject from being enrolled into the study:

1. Has significant neurological disease, other than a-MCI that may affect cognition.
2. History of clinically evident stroke or history of clinically significant carotid or vertebrobasilar stenosis or plaque.
3. History of seizures, excluding febrile seizures in childhood.
4. History of screening visit brain MRI scan indicative of any other significant abnormality, including but not limited to multiple microhemorrhages (2 or more), history or evidence of a single prior hemorrhage > 1 cm3, multiple lacunar infarcts (2 or more) or evidence of a single prior infarct > 1 cm3, evidence of a cerebral contusion, encephalomalacia, aneurysms, vascular malformations, subdural hematoma, or space occupying lesions of significance as determined by the PI (e.g., arachnoid cysts or brain tumors such as meningioma).
5. Brain MRI shows moderate or severe cortical or hippocampal atrophy.

6. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, CSF shunts, claustrophobia, metal fragments or foreign objects in the eyes, skin, or body that would contraindicate a brain MRI scan.
7. Current presence of a clinically significant major psychiatric disorder (eg., Major Depressive Disorder) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) or symptom (eg., hallucinations) that could affect the subject's ability to complete the study.
8. Current clinically significant systemic illness that is likely to result in deterioration of the subject's condition or affect the subject's safety during the study including but not limited to renal failure or myocardial infarction.
9. History of cancer within the last 5 years, with the exception of nonmetastatic basal cell carcinoma, and squamous cell carcinoma of the skin.
10. Uncontrolled hypertension (diastolic BP> 100 mmHg or systolic BP> 160 mmHg, sitting).
11. History or evidence of any clinically significant autoimmune disease or disorder of the immune system (eg., Crohn's Disease, Rheumatoid Arthritis)
12. Clinically significant infection within the last 30 days (eg., chronic persistent or acute infection (eg., upper respiratory infection [URI], urinary tract infection [UTI]).
13. Women of childbearing potential.
14. Other clinically significant abnormality on physical, neurological, laboratory, vital signs or ECG examination (eg., atrial fibrillation) that could compromise the study or be detrimental to the subject.
15. Weight greater than 120 kg (264 lbs).
16. Excessive smoking defined as more than 20 cigarettes per day.
17. History of alcohol or drug dependence or abuse as defined by DSM-IV criteria within the last 2 years.
18. Severe liver or kidney disease verified by the PI review of ALT, AST and creatinine.
19. Known coagulopathy, thrombosis, or low platelet count.
20. Hemoglobin less than 11 g/dL.
21. Known deficiency to IgA.
22. Positive serology for Hepatitis B or C, or HIV.
23. Concurrent treatment with cholinesterase inhibitors, memantine, Axona, or other prescription cognitive enhancing agents, or discontinuation of any of these agents within 90 days prior to screening.
24. Current use of nonprescription medication or cognitive enhancing agents within 30 days prior to screening including but not limited to herbal preparations, gingko biloba, and huperzine.
25. Concurrent use of anticholinergic drugs including diphenhydramine.
26. Current use of anticonvulsant drugs for seizures, antiparkinson drugs, anticoagulant medications (except the use of aspirin 325 mg/day or less, plavix, aggrenox, and persantine but not for stroke).

27. Concurrent use of opioid pain relievers and related synthetic derivatives.
28. Unless maintained on a stable dose regimen for at least 30 days prior to screening, any other medications with the potential to affect cognition/behavior (e.g. anti-depressant medication, sleep-aid medication)
29. Treatment with immunosuppressive medications (eg., systemic corticosteroids) within the last 90 days (topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted) or chemotherapeutic agents for malignancy within the last 3 years.
30. Use of experimental medications for AD or any other investigational medications or devices for treatment of indications other than AD within 60 days prior to screening or within 5 half-lives of use of such a medication prior to screening, whichever is longer.
31. Prior treatment with IVIG or other experimental immunotherapeutic or vaccine for MCI or AD, or prior treatment with a biological product for the treatment of a-MCI or AD.
32. Live viral vaccination within 1 month prior to screening, or until at least 3 months after receiving the last dose of study drug.
33. Subjects who have donated blood (routine blood donation) in the 30 days prior to screening.
34. Any known hypersensitivity to any of the excipients contained in the study drug formulation.
35. Religious objection to the use of human products.

5.0 SUBJECT RANDOMIZATION AND ENROLLMENT

Prior to the start of enrollment, the following critical documents must be filed in the sponsor's regulatory binder (trial master file):

- Investigational new drug (IND) application approved by the FDA
- Sutter Health Central Institutional Review Committee (SHCIRC) approval of the study protocol and the informed consent form (ICF)
- Signed and dated study protocol
- Completed Federal Drug Administration (FDA) Form 1572
- Current curricula vitae and medical licenses (if applicable) of the Principal Investigator (PI) and all Sub-Investigators listed on the Form FDA 1572;
- Name, address, and membership of the IRB, and/or written statement that IRB is properly constituted and operates according to Good Clinical Practices (GCP)
- Investigator's Brochure
- Laboratory normal range and documentation of laboratory certification (or equivalent).

5.1 Randomization

Once subjects have satisfied all subject selection criteria and signed an informed consent, they may be randomized. The randomization scheme will be developed by the research scientist. The research pharmacist will receive the randomization assignment from the research scientist. Subjects will be randomized (1:1) by the research pharmacist to receive

either NewGam 10% 0.4 g/kg or 0.9% saline placebo once every 14 days for two months for a total of five infusions.

5.2 Enrollment

A subject is considered enrolled when they have been randomized and received any amount of study medication (i.e., IVIG or placebo) by infusion.

6.0 STUDY DRUG AND TREATMENT

6.1 Description of study drug

NewGam, the current working title for a new IVIG formulation, is a newly developed 10% human normal immunoglobulin solution ready for intravenous administration. Adverse Drug Reactions (ADRs) reported for NewGam are expected to be similar in type and intensity to those reported with other IVIG preparations.

The NewGam manufacturing process achieves a significant viral reduction through a combination of two dedicated manufacturing process steps: solvent/detergent (S/D) treatment and nanofiltration (20 nm). Based on the combination of these two steps, NewGam complies with the latest international consensus on best practices for viral safety. The Source Q chromatography (ion-exchange chromatography) step in the NewGam process also contributes significantly to the viral safety of NewGam. The efficacy of the virus inactivation procedures has been extensively validated according to relevant international guidelines in place. Further information can be found in the current Investigator's Brochure.

6.2 Shipping, handling, and storage

IVIG will be shipped directly to the pharmacy or investigational site, after all required regulatory and legal documents have been received by the Sponsor.

Upon receipt of the study drug shipments, the unblinded pharmacist will verify the condition of the study drug and perform study drug accountability. Acknowledgement of receipt will be documented in the Pharmacy Binder. A temperature logger showing the transport temperature will be read out by the shipper and release the drug if the transport temperature is verified to be between +2°C to + 8°C (36°F to 46°F). If there was a deviation from this temperature range, an Octapharma Project Manager or Qualified Person must assess the temperature log and approve release.

The study drug will be stored in a secure area with access restricted only to authorized personnel. NewGam may be stored for 15 months at +2°C to + 8°C (36°F to 46°F) from the date of manufacture.

6.3 Special precautions for storage

- Do not freeze. Frozen product should not be used
- Do not use after expiration date
- Other than the unblinded pharmacist, all other site personnel are fully blinded and may not handle, store or dispense study drug

6.4 Drug accountability

The investigator is responsible to ensure supervision of accurate monitoring of the receipt, storage and allocation of the study drug. Copies of all invoices of study drug shipments must be retained. Accurate study drug inventory, dispensing and accountability logs must be obtained and stored in the Pharmacy Binder.

6.5 Blinding and unblinding

The study coordinator, investigator, and infusion nurse will be blinded to whether the subject is receiving placebo or NewGam. The pharmacist will receive the assignment from the research scientist who will develop the randomization scheme. Both will know of the subject's treatment assignment. While participating in the study, a subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further medical management of the subject. Unblinding for any other reason during the study will be considered a protocol violation.

Subjects participating in the extension portion of the study may be unblinded upon study completion (Visit 15/month 60). Subjects declining participation in the extension portion of the study or subjects not completing the study will be unblinded upon request.

6.6 Study drug dosage

The dose level of IVIG at 0.4 g/kg or 0.9% saline placebo will be administered by IV infusion once every 14 days for two months. There is no provision for dose adjustments by the investigator under this protocol.

6.7 Study drug preparation and infusion

- The unblinded pharmacist will prepare the IVIG or placebo for each infusion.
- The IVIG should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid and/or discoloration is observed.
- The IVIG must not be mixed with other medicinal products or administered simultaneously with other intravenous preparation in the same infusion set. Do not mix with IVIG products from other manufacturers.
- Do not freeze. Solutions that have been frozen should not be used.
- IVIG bottle is for single use only. NewGam contains no preservative. Any bottle that has been entered should be used promptly. Partially used bottles should be discarded.
- Content of IVIG bottles may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling (within 72 hours if stored at 2-8°C [36-46°F]).
- Do not use after expiration date.
- IVIG should not be diluted.
- IVIG must be allowed to warm to room or body temperature prior to infusion if stored at 2-8°C (36-46°F).
- 0.4 g/kg body weight of Newgam 10% or 0.9% saline placebo is transferred into an EVA infusion bag.
- The infusion bag must be covered with a dark hood and dark infusion lines attached prior to infusion to maintain the study blind.

6.8 Incompatibilities

- NewGam must not be mixed with other medicinal products or administered simultaneously with other intravenous preparations in the same infusion set.

6.9 Administration

- IVIG should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid and/or discoloration is observe
- IVIG should be at room or body temperature during administration. Only administer intravenously.
- Any bottle that has been opened should be used promptly. Partially used bottles should be discarded.
- NewGam is not supplied with an infusion set. If an in-line filter is used the pore size should be 0.2 – 200 microns.
- Do not use a needle of larger than 16 gauge to prevent the possibility of coring. Insert needle only once, within the stopper area delineated (by the raised ring for penetration). The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

6.10 Rate of administration

The initial infusion rate of IVIG (NewGam) or placebo will be 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes; if tolerated, advanced to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes; if tolerated, advanced to 0.03 mL/kg/min (180 mg/kg/hr) for the second 30 minutes and, if tolerated, advanced to 0.04 mL/kg/min (240 mg/kg/hr) for the remaining time at the discretion of the treating Investigator.

If adverse events (AEs) occur during infusion, the rate should be reduced to half the rate at which the event occurred, or the infusion interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient.

The batch number(s) and number of different vial sizes used will be recorded on the drug accountability form.

6.11 Concomitant therapy

6.11.1 *Prohibited*

During the course of the study, experimental medications for MCI or AD and all other experimental medications are prohibited. Subject must refrain from using any medication, vitamin, or herbal supplement considered to enhance cognition or indicated for a-MCI or AD unless approved by the investigator. Prohibited medications, vitamins and herbal supplement included but are not limited to cholinesterase inhibitors, memantine, Axona, ginko biloba, and huperzine.

6.11.1 *Permitted*

Concomitant medications will be assessed at all study visits. Concomitant medications are prescribed or over-the-counter medications and should be consistent with the inclusion/exclusion criteria. Concomitant medication appropriate to the subject's condition may be prescribed during the course of the study with the exception of those listed above.

Routine vaccinations (i.e., flu vaccination) with commercially available therapeutics are permitted but must not be given within four weeks before or after the administration of the study drug. No vaccination for a-MCI or AD is allowed during the course of the study.

7.0 EVALUATIONS BY VISIT

The overall summary of study activities by visit is provided in Appendix C at the end of the document.

Screening procedures at visit 1 will take place up to 28 days prior to Visit 2 (Day 1) dosing. Screening labs and assessments will be performed during the screening period. A brain MRI will be obtained as standard of care within 6 months prior to the screening period. The first dose of study drug is administered on Day 1. Visits 2 through 6 have a ±1 day window and occur every 14 days over two months. The investigator will determine if a subject is suitable to continue following the missed infusion. Visits 7 through 12 (Month 4 through Month 24) have a ±7 day window. Visits 13 through 15 (Month 36 through Month 60) have a ±14 day window).

All study screening data from Visit 1 including laboratory results must be reviewed for study eligibility prior to receiving first dose of study drug. Visit 2 physical exams and neurological exams prior to infusion may occur within 72 hours prior to the first infusion. Prior to infusion, a review of concomitant medications and AEs takes place to ensure that no excluded medications have been added or medication discontinued or dose changed that were required to have been stable. If the subject continues to be eligible for enrollment, the subject will be randomized, infused with study medication and will remain in the infusion clinic for at least 4 hours following the start of the infusion for safety assessments on Visit 2 (Day 1).

7.1 VISIT 1: Screening

The following screening procedures will occur up to 28 days prior to Visit 2 (Day 1) infusion:

- Obtain signed and dated SHCIRC approved written Informed Consent from the subject and collaborative informant prior to the initiation of any screening procedure
- Assess Inclusion/Exclusion criteria
- Obtain medical history
- Record prior medications
- Assess Petersen criteria for mild cognitive impairment
- Determine Rosen Modified Hachinski Ischemic score
- Record vital signs
- Perform physical examination including height and weight
- Perform neurological examination
- Obtain standard 12-lead ECG
- Obtain a brain MRI according to Appendix E for clinical assessment, ventricular volume, and review the scan for evidence of vasogenic edema, microhemorrhage, infarction or other clinically significant abnormality
- Perform lumbar puncture to obtain CSF Aβ1-42/CSF P-Tau_{181P}
- Administer MMSE, ADAS-Cog, and CDR-SB
- Obtain blood sample for ApoE genotyping, IgA deficiency, serum viscosity

- Obtain blood sample for complete blood count (CBC) and comprehensive metabolic panel (chemistry panel). (Appendix D)
- Obtain blood sample for thyroid stimulating hormone (TSH), vitamin-B12 and rapid plasma reagin laboratory tests
- Obtain blood sample for HIV-I & II, HCV, HBV, B19, HAV
- Obtain urine sample for routine urinalysis

7.2 VISIT 2: Day 1 – First Infusion

The investigator will confirm that subjects are still eligible by reviewing all screening data. Subjects who no longer meet criteria will not be eligible for enrollment in the study.

7.2.1 Pre-dose:

- Confirm that subjects continue to meet inclusion/exclusion criteria
- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations (may occur within 72 hours prior to first infusion)
- Complete randomization
- The unblinded pharmacist will prepare the study drug according to the preparation instructions in Section 5.7 and will deliver the study drug to the blinded infusion administration site.

7.2.2 Study drug infusion:

- Subjects will be given the option of prophylaxis oral acetaminophen, diphenhydramine, or both 15-30 minutes prior to infusion
- Measure blood pressure, pulse rate, temperature and respiratory rate within 15 minutes prior to start of the infusion
- Administer study drug to the subject by intravenous infusion

7.2.3 Following initiation of infusion:

- Measure blood pressure and pulse rate at 15, 30, 60 and every 30 minute mark for the duration of the infusion
- Measure blood pressure, pulse rate, temperature and respiratory rate immediately post dose and prior to leaving the clinic
- Assess infusion site post infusion
- Assess and record AEs
- Subjects will remain in the clinic for at least one hour following the completion of the infusion. The subjects may leave the clinic after the observation period if the subject is medically stable.

7.3 VISIT 3 (Day 14 -Second Infusion) through VISIT 6 (Day 56 – Fifth Infusion)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- If there is any abnormality of vital signs or clinical concerns during infusion visit, the principle-investigator or sub-investigator will be paged in order to perform a clinical assessment.
- The unblinded pharmacist will prepare the study drug according to the preparation instructions and will deliver the study drug to the blinded infusion administration

7.3.1 Study drug infusion:

- Subjects will be given the option of prophylaxis oral acetaminophen, diphenhydramine, or both 15-30 minutes prior to infusion
- Measure blood pressure, pulse rate, temperature and respiratory rate within 15 minutes prior to start of the infusion
- Administer study drug to the subject by intravenous infusion

7.3.2 Following initiation of infusion:

- Measure blood pressure and pulse rate at 15, 30, 60 and every 30 minute mark for the duration of the infusion
- Measure blood pressure, pulse rate, temperature and respiratory rate immediately post infusion and prior to leaving the clinic
- Assess infusion site post infusion
- Assess and record AEs
- Subjects will remain in the clinic for at least 15 minutes following the completion of the infusion. The subjects may leave the clinic after the observation period if the subject is medically stable.

7.4 VISIT 7: Month 4 (±7 days)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Record vital signs
- Assess and record AEs
- Record concomitant medications
- Obtain standard 12-lead ECG
- Administer MMSE, ADAS-Cog, and CDR-SB
- Obtain blood sample for routine hematology and chemistry laboratory tests
- Obtain blood sample for HIV-I & II, HCV, HBV, B19, HAV

7.5 VISIT 8: Month 8 (±7 days)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Administer MMSE, ADAS-Cog, and CDR-SB
- Obtain blood sample for HIV-I & II, HCV, HBV, B19, HAV

7.6 VISIT 9: Month 12 (±7 days) - 12 months after baseline

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Obtain a brain MRI according to Appendix E for clinical assessment, ventricular volume, and review the scan for evidence of vasogenic edema, microhemorrhage, infarction or other clinically significant abnormality
- Perform physical and neurological examinations
- Administer MMSE, ADAS-Cog, and CDR-SB
- Obtain blood sample for routine hematology and chemistry laboratory tests

7.7 VISIT 10: Month 16 (±7 days)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Administer MMSE, ADAS-Cog, and CDR-SB

7.8 VISIT 11: Month 20 (±7 days)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Administer MMSE, ADAS-Cog, and CDR-SB

7.9 VISIT 12: Month 24 (±7 days) - 24 months after baseline

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Obtain standard 12-lead ECG
- Obtain a brain MRI according to Appendix E for clinical assessment, ventricular volume,

and review the scan for evidence of vasogenic edema, microhemorrhage, infarction or other clinically significant abnormality

- Administer MMSE, ADAS-Cog, and CDR-SB
- Obtain blood sample for routine hematology and chemistry laboratory tests

7.10 VISIT 13: Month 36 (±14 days) – 36 months after baseline (extension visit)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Obtain a brain MRI according to Appendix E for clinical assessment, ventricular volume, and review the scan for evidence of vasogenic edema, microhemorrhage, infarction or other clinically significant abnormality
- Administer MMSE, ADAS-Cog, and CDR-SB

7.11 VISIT 14: Month 48 (±14 days) – 48 months after baseline (extension visit)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Obtain a brain MRI according to Appendix E for clinical assessment, ventricular volume, and review the scan for evidence of vasogenic edema, microhemorrhage, infarction or other clinically significant abnormality
- Administer MMSE, ADAS-Cog, and CDR-SB

7.12 VISIT 15: Month 60 (±14 days) – 60 months after baseline (extension visit)

- Assess and record AEs
- Record concomitant medications
- Record vital signs
- Perform physical and neurological examinations
- Obtain a brain MRI according to Appendix E for clinical assessment, ventricular volume, and review the scan for evidence of vasogenic edema, microhemorrhage, infarction or other clinically significant abnormality
- Administer MMSE, ADAS-Cog, and CDR-SB

7.13 Early termination from the study

Every attempt should be made to follow each subject through the final visit 12, and subsequently visit 15 of the extension study. In the event of early withdrawal from the subject for any reason, an Early Termination Visit should be completed for criteria of withdrawal. If the subject withdraws due to an AE, every attempt should be made to follow the subject until the AE resolves or until the investigator deems that the AE is stable or determined the AE to be chronic. All SAEs will continue to be followed until the end of the study (Visit 12, 15, or ET visit) or until the SAE has resolved or the investigator deems the event to be stable or chronic.

8.0 CONVERSION TO ALZHEIMER DISEASE

Patients who convert to AD will have the choice of remaining in the study on a modified follow-up visit schedule, or may withdraw from the study. Depending on when the conversion occurs, the subjects will be asked to complete the following:

- Complete all Visit 7 study activities described above
- Complete *only the following* for Visit 8:
    1. HIV-I & II, HCV, HBV, B19, HAV
    2. Adverse events and Concomitant Meds
- Complete all Visit 9 study activities described above
- Subjects will not attend Visit 10 and Visit 11
- Complete all Visit 12 study activities
- Complete all Visit 13, 14, and 15 study activities (optional)

Patients who convert to Alzheimer Disease will be followed for safety reasons, to determine rate of conversion between groups, and to track any continued changes in ventricular volume between the 0.4 g/kg NewGam or 0.9% saline solution (placebo) groups.

9.0 WITHDRAWAL AND REPLACEMENT OF SUBJECTS

9.1 Criteria for subject withdrawal

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason. If a subject requests or decides to withdraw, every attempt will be made to complete an early termination visit.

The investigator has the right to withdraw subjects from the study if a subject:

- Is in significant violation of the protocol
- Experiences an intolerable AE or SAE
- Is non-compliant
- Withdrawal of consent
- Lost to follow up
- Death

9.2 Replacement of subjects

Subjects screened but not randomized will be replaced. Subjects withdrawn after receiving the third infusion will not be replaced but will be followed if they provide consent.

10.0 ADVERSE EVENTS

10.1 Adverse event definition

An AE is any untoward event that occurs any time after randomization to the double blind treatment until the end of study (visit 12, visit 15, or ET visit). The event need not have a causal relationship with the study drug or treatment. Adverse events include, but are not limited to clinically significant changes in clinical status, physical or neurological examinations, ECG, abnormal laboratory findings, exacerbations of underlying disease, and drug interactions,

dependency, misuse and abuse. All AEs must be documented on the Adverse Event page of the CRF and in the subject's medical notes. Each AE is evaluated for duration, severity, seriousness, relatedness to study drug, and action taken. The investigator may be asked to provide follow-up information.

10.2 Serious adverse event (SAE) definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly/birth defect
- Is a medically important condition:

  Suspected transmission of an infectious agent,

  Thromboembolic events,

  Cerebral hemorrhage resulting in clinical disability, or

  Other reactions that should be reported in an expedited manner although they did not immediately result in one of the above seriousness criteria

10.3 Other relevant drug safety information:

Any safety information relating to

- Pregnancies/breastfeeding,
- Drug abuse (persistent, sporadic or intentional excessive use of a medicinal product inconsistent with the SPC or acceptable medical practice),
- Overdose (treatment exceeding the medically recommended dose),
- Medication errors (prescribing or dispensing error),
- Interactions with other medicinal products or devices
- Associated with NewGam 10%, even if no adverse drug reaction occurred.

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

10.4 Adverse events severity

Severity of AEs will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (**http://ctep.info.nih.gov**). AEs not corresponding to the CTCAE term will be assessed according to their impact on the subject's ability to perform daily activities as follows:

- Mild (grade 1) – the AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
- Moderate (grade 2) – the AE produces some impairment of functioning, but is not hazardous to health. It is uncomfortable or an embarrassment.
- Severe (grade 3) – the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.
- Life Threatening (grade 4) – Life threatening or disabling.
- Fatal (grade 5) Causes death of the participant.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

10.5 Adverse event reporting

All AEs, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up form. A final report to document resolution of the adverse event is required.

10.6 Investigator reporting to the FDA

Adverse drug reactions that are **serious, unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the FDA in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The investigator/physician shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug as soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

10.7 Reporting of adverse drug reactions and other safety information to study supporter

All suspected AEs and other safety information associated with the administration of NewGam have to be reported to:

Central Drug Safety Unit:

Email: cdsu@octapharma.com

Fax: +43-1-61032-9949

Serious adverse drug reactions have to be reported immediately by fax or email (within 24 hrs). Non-serious adverse drug reactions and other safety information should be reported to Octapharma, if possible, upon recognition but no later than 10 days.

10.8 Report of adverse events to the institutional review board

The principal investigator is required to notify the Sutter Health Institutional Review Committee (SHCIRC) of a serious adverse event according to institutional policy.

10.9 Reporting of adverse drug reactions and other safety information to study sponsor

Octapharma shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in any studies involving Newgam 10% that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

10.10 Adverse event updates

The investigator must keep copies of all AE information, including correspondence with Octapharma and the SHCIRC, on file.

The investigator shall notify the SHCIRC promptly of any new serious and unexpected AE(s) or significant risks to subjects.

11.0 IND ANNUAL REPORTS

The conduct of the study will comply with all FDA safety reporting requirements.

11.1 IND annual reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Octapharma as a supporter of this study as follows:

Octapharma Pharmazeutika Produktionsges.m.b.H

attn: Dr. Barbara Rangetiner (Head Int. Drug Regulatory affairs)

Oberlaaer Strasse 235

A-1100 Vienna, Austria

All AE reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present.

2.0 12.0 RESPONSE CRITERIA

The MMSE, CDR-SB, and ADAS-cog are scheduled to occur at 4, 8, 12, 16, 20, 24, 36, 48, and 60 months after Visit 1.

3.0 13.0 PROTOCOL DEVIATIONS

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the SHCIRC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the principal investigator.

14.0 DATA RECORDING, RETENTION, AND MONITORING

14.1 Data entry and maintenance

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Study personnel will construct case report forms (CRFs), record all study data onto the CRFs and enter the data into a 21 CFR Part 11 compliant database.

14.2 Study records retention

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The investigator agrees to adhere to the document/records retention procedures by signing the protocol.

14.3 Data monitoring committee

The Data Monitoring Committee (DMC) will be composed of independent reviewers who will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DMC is to advise on serious safety considerations, lack of efficacy, and any other considerations within the charge to the Committee. The DMC may request additional meetings or safety reports as deemed necessary upon discussion with the investigator or Octapharma and its representatives. The DMC may stop the study following review of results from the interim analysis.

15.0 STATISTICAL ANALYSIS

15.1 Primary endpoint

The aim of the primary efficacy analysis is to demonstrate an advantage for subjects treated with IVIG over subjects treated with placebo at the end of the study as measured by change in ventricular volume. The primary efficacy analyses will be performed on the intent-to-treat (ITT) population. The ITT population is defined as all subjects who were randomized, received three or more infusions, and had a brain MRI at baseline and at 24 months.

Annualized percent change in total ventricular volume (APCV) is the primary biomarker of interest. Brain MRI will be obtained at baseline, 12 months, 24 months, 36 months, 48 months, and 60 months. Differences between the IVIG and placebo group at month 12, 24, 36, 48, and 60 will be analyzed using a 2 x 2 analysis of variance. Participants will also be classified as early MCI (EMCI) if baseline CDR-SB is less than 1.5, and late MCI (LMCI) if CDR-SB is greater than or equal to 1.5.

Treatment (IVIG, placebo), MCI status (EMCI, LMCI), and the treatment X MCI status interaction will be included in the model. If the interaction is statistically significant ($p < 0.05$), MCI status will be stratified and differences in APCV between the groups compared within each stratum.

15.2 Secondary Endpoints

15.2.1 Conversion to AD

Conversion to AD is measured by NINCDS-ADRDA and NIA [14] criteria for diagnosis of Alzheimer Disease and Clinical Dementia Rating (CDR) (Appendix A).

Kaplan-Meier survival curves will be estimated and will plot the proportion of treatment and control subjects who remain without a diagnosis of AD at month 24, 36, 48, and 60. The log-rank test will be used to determine whether the survival curves are different for the two groups of subjects. Cox proportional hazards will be used to assess the incidence of AD in treatment versus control subjects adjusting for age and sex.

15.2.2 Cognitive change

The CDR-SB, MMSE, and ADAS-cog are administered at baseline and at months 4, 8, 12, 16, 20, 24, 36, 48, and 60. Separate linear mixed-effects modeling will be used to compare differences in the scores on each these tests using all available observations. Treatment (IVIG/placebo), MCI status (early, late), and treatment X MCI status will be fixed factors and the respective baseline score will be included as the continuous covariate. For statistically significant ($p < 0.05$), interactions, MCI status will be stratified and the analyses will be conducted for each stratum.

Data will be analyzed to assess safety after 25 subjects complete three months of follow-up. Safety will be evaluated though documentation of adverse events. Appropriate safety data summaries will be provided to the DSMC after each interim analysis.

15.2.3 CSF Aβ1-42/CSF P-Tau$_{181P}$ Alzheimer signature

Annualized percent change in ventricular volume between the IVIG and placebo group at month 12, 24, 36, 48, and 60 will be also analyzed specifically in subjects with positive CSF Aβ1-42/CSF P Tau$_{181P}$ Alzheimer signature.

16.0 SAMPLE SIZE AND POWER FOR PRIMARY ENDPOINT

Twenty-five subjects will be randomized to placebo and 25 subjects will be randomized to the group receiving IVIG. Twenty-five subjects in each group provides 82% power to detect a 120 unit difference in mean ventricular volume between the groups at month 26. This calculation is based on a two-sided test with alpha set at 0.05.

17.0 IMPLICATIONS AND DIRECTION FOR FUTURE STUDIES

This study is designed to assess the efficacy of the smallest reasonable dose of IVIG that could prevent ventricular atrophy in patients with a-MCI. Subjects will receive IVIG 0.4g/kg every 2 weeks as the half-life of IVIG antibodies has been reported as 9.3 days [8]; furthermore Relkin [8] found the dosing schedule of 0.4/kg every 2 weeks to be most effective in reducing brain atrophy. [9] We decided to study the smallest reasonable course of IVIG which would be 5 total treatments as a 2g/kg total treatment dose is standard dose used for other indications of IVIG (including neurological disorders). IVIG has not been investigated in a-MCI and we hypothesis that patients with early Alzheimer's pathology may require smaller doses of IVIG. Furthermore if effective, this short course would both reduce the risk of IVIG treatment adverse events and reduce cost of treatment. Both of the former would increase accessibility of this treatment to patients with a-MCI. At the end of the two years we plan to perform an add-on study with participating subjects to include an additional three years of follow-up (five years total).

If the results of this exploratory study are found at the end of two years to show a trend towards positive efficacy with this treatment strategy, the current study may be expanded to include more subjects with dose-ranging investigations or the results used to design a large, multi-arm randomized trial.

18.0 ETHICAL AND LEGAL ISSUES

The study will be submitted to the SHCIRC. A data safety monitoring committee will be convened to provide oversight of subjects' safety before commencement of the study.

18.1 Institutional review board approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the SHCIRC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The investigator will be responsible for preparing documents for submission to the SHCIRC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of SHCIRC approval must be submitted by the Investigator to the SHCIRC for approval. The Investigator is also responsible for notifying the SHCIRC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the SHCIRC prior to use.

18.2 Informed consent

The investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the investigator's study files.

18.3 Subject confidentiality

Octapharma affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Octapharma requires the investigator to permit Octapharma representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

18.4 Protocol amendments

Any amendment to this protocol must be agreed to by the principal investigator and reviewed by Octapharma. Amendments should only be submitted to the SHCIRC after consideration of Octapharma review. Written verification of SHCIRC approval will be obtained before any amendment is implemented.

18.5 Premature discontinuation of study

The responsible local clinical investigator and Octapharma have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.
- Statistical analysis demonstrates overwhelming efficacy of treatment.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., SHCIRC/EC, regulatory authorities, etc.).

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20.0 APPENDIX A.

20.1 NINCDS-ADRDA criteria for diagnosis Alzheimer Disease [16]

- Dementia established by clinical examination and documented by the Mini-Mental State Test, Blessed Dementia Scale or some similar examination, and confirmed by neuropsychological tests
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65
- Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

20.1.1 The diagnosis of probable Alzheimer disease is supported by:

- Progressive deterioration of specific cognitive skills such as language (aphasia), motor skills (apraxia), and perception (agnosia)
- Impaired activities of daily living and altered patterns of behavior
- Family history of similar disorders, particularly if confirmed neuropathologically
- Laboratory results of:
    1. Normal lumbar puncture as evaluated by standard techniques
    2. Normal pattern or nonspecific changes in EEG, such as increased slow-wave activity
    3. Evidence of cerebral atrophy on CT with progression documented by serial Observation

20.1.2 Other clinical features consistent with the diagnosis of probable Alzheimer disease, after exclusion of causes of dementia other than Alzheimer disease:

- Plateaus in the progression of the illness
- Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations; catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss
- Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder
- Seizures in advanced disease
- CT normal for age

20.1.3 Features that make the diagnosis of probable Alzheimer disease uncertain or unlikely include:

- Sudden, apoplectic onset

- Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
- Seizures or gait disturbances at the onset or very early in the course of the illness

20.1.4 5. Criteria for diagnosis of definite Alzheimer disease are:

- The clinical criteria for probable Alzheimer disease and, in addition, histopathological evidence obtained from a biopsy or autopsy.

21.0 APPENDIX B

21.1 Criteria for amnestic mild cognitive impairment [17]

- Memory complaint usually corroborated by an informant
- Objective memory impairment for age
- Essentially preserved general cognitive function
- Largely intact functional activities
- Not demented

22.0 APPENDIX C

22.1 Schedule of study activities

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Study Time Point	Day -28 To Day -1	D1	D14	D28	D42	D56	M4	M8	M12	M16	M20	M24 /ET[6]	M36	M48	M60 /ET[7]
Visit Type (Visit Window)	Screening	Infusion Visits (±1 day)					Follow-up (±7 days)						Follow-up (±14 days)		
CLINICAL															
Informed consent	X														
Inclusion/Exclusion	X	X													
Medical Hx/Prior/Baseline Medications	X														
a-MCI Petersen/NIA criteria review	X														
Modified Hachinski Ischemia Scale	X														
ApoE4 genotyping[1]	X														
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X[2]					X	X	X	X	X	X	X	X	X
Neurological Exam	X	X[2]					X	X	X	X	X	X	X	X	X
ECG	X						X					X			
Brain MRI	X								X			X	X	X	X
CSF-amyloid protein 1-42 tau 181P biomarker mixture (Optional)	X														
Mini Mental State Exam (MMSE)	X						X	X	X	X	X	X	X	X	X
CDR-SB, ADAS-cog	X						X	X	X	X	X	X	X	X	X
HIV-I & II, HCV, HBV, B19[3], HAV[3]	X						X	X							
IGA deficiency	X														
Serum viscosity	X														
CBC, Chemistry Panel (Appendix B)	X						X		X			X			
TSH, Vit-B12, RPR[4]	X														
Urinalysis[5]	X														
Adverse events & Concomitant Meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Study Time Point	Day -28 To Day -1	D1	D14	D28	D42	D56	M4	M8	M12	M16	M20	M24/ ET[6]	M36	M48	M60 /ET[7]
Visit Type (Visit Window)	Screening	Infusion Visits (±1 day)					Follow-up (±7 days)						Follow-up (±14 days)		
THERAPY															
Randomization		X													
Infusion of IVIG or placebo		X	X	X	X	X									
Assess infusion site		X	X	X	X	X									

[1] Previous ApoE4 testing will be accepted

[2] Exams may occur within 72 prior to infusion

[3] Performed at 4 and 8 months only if subject is negative at baseline

[4] RPR required if not done in the last 12 months prior to screening

[5] Urine culture may be performed if indicated

[6] Early Termination visit for subjects in the two study (Section 7.13)

[7] Early Termination visit for subjects in the three year extension study (Section 7.13)

23.0 APPENDIX D.

23.1 Clinical laboratory tests

Comprehensive Metabolic Panel	Complete Blood Count with differential	Urinalysis
Sodium	WBC	Urine microscopy
Potassium	RBC	Culture if indicated
Chloride	Hemoglobin	
CO2	Hematocrit	
Glucose	MCV	
BUN	MCH	
Creatinine	RDW	
Calcium	Platelet Count	
Total Protein	Neutrophil %	
Albumin	Lymphocytes %	
Total Bilirubin	Monocyte %	
Alkaline Phosphatase	Eosinophil %	
AST	Basophil %	
ALT	Neutrophil Count	
	Lymphocyte Count	
	Monocyte Count	
	Eosinophil Count	
	Basophil Count	

24.0 APPENDIX E. BRAIN MRI IMAGING INSTRUCTIONS

Equipment: Siemens 3.0 Tesla Verio

Software B17

Hardware TIM system

Coil: Matrix Head coil

Installed Install 2010

Next scheduled software upgrade; B17 5/2010

Neuro Imaging Protocol of the Brain: Head Matrix Coil

Sequence 1: 3 plane localizer-2D GRE

Sequence 2: Sagittal 3D MPRAGE

Sequence 3: Sagittal T1 Flair

Sequence 4: Axial T2

Sequence 5: Axial GRE

Sequence 6: Axial FLAIR

Sequence 7: Axial DWI

Sequence 8: Axial T1

Sequence 9: Coronal T2 3.0 mm

25.0 AMENDMENT 1: FEBRUARY, 2011

25.1 AMENDMENT 1: INTRODUCTION

The mains reason for protocol amendment 1 are to revise exclusion criteria 23, Appendix E Brain MRI Instructions and administrative changes.

25.2 AMENDMENT 1: SUMMARY OF CHANGES

Section 4.2 Exclusion Criteria – Exclusion 23

Changed from:

23. Concurrent or prior treatment with cholinesterase inhibitors and/or memantine, or Axona for cognitive enhancement. Exceptions (e.g. brief exposure to one of these medications) may be authorized if agreed upon by PI and sub-I)

Changed to:

23. Concurrent treatment with cholinesterase inhibitors, memantine, Axona, or other prescription cognitive enhancing agents, or discontinuation of any of these agents within 90 days prior to screening.

Rationale: Exclusion 23 was originally included because it may clinicians have proposed cholinesterase inhibitors and memantine may improve cognitive function in patients with MCI. We did not want this to confound the results of the study. A study published in the *Archives of Neurology* in January, 2011 found that cholinesterase inhibitors or memantine were not associated with clinical improvement and may alternatively be associated with a decline in patients with MCI. This information, coupled with the fact the so many practitioners have started patients with MCI on these medications which makes recruitment of medication-naive patients difficult, led us to amend this exclusion. Therefore, we are allowing enrollment of patients previously exposed to cholinesterase inhibitors and memantine after a 90 day wash-out.

Section 7.2.2 Study Drug Infusion and Section 7.3.1 Study Drug Infusion

Updated language in bold: Subjects will be given the option of prophylaxis oral acetaminophen, diphenhydramine, or both 15**-30** minutes prior to infusion

Rationale: Standard of care is give prophylaxis medications 30 minutes prior to start of infusion.

Section 7.3.3 One hour following final infusion at Visit 6

Section was completely removed since visits 3 through 6 require the subject to stay at clinic for 15 minutes post infusion.

Appendix E. Brain MRI imaging instructions

Changed from:

Equipment: Siemens 1.5 Tesla Avanto

Software B15

Hardware TIM system

Coil: Matrix Head coil

Installed Install 2006

Next scheduled software upgrade; B17 5/2010

Neuro Imaging Protocol of the Brain: Head Matrix Coil

Sequence 1: 3 plane localizer-2D GRE

Sequence 2: Sagittal 2D SE

Sequence 3: Sagittal 3D MPRAGE T1

Sequence 4: Axial 2D TSE

Sequence 5: Axial Flair TIR

Sequence 6: Axial T2* 2D GRE

Sequence 7: Axial DWI 2D EPI

Sequence 8: Coronal T2 Flair

Changed to:

Equipment: Siemens 3.0 Tesla Verio

Software B17

Hardware TIM system

Coil: Matrix Head coil

Installed Install 2010

Next scheduled software upgrade; B17 5/2010

Neuro Imaging Protocol of the Brain: Head Matrix Coil

Sequence 1: 3 plane localizer-2D GRE

Sequence 2: Sagittal 3D MPRAGE

Sequence 3: Sagittal T1 Flair

Sequence 4: Axial T2

Sequence 5: Axial GRE

Sequence 6: Axial FLAIR

Sequence 7: Axial DWI

Sequence 8: Axial T1

Sequence 9: Coronal T2 3.0 mm

Rationale: Updated information for the MRI equipment.

26.0 AMENDMENT 2: MARCH 2011

26.1 AMENDMENT 2: INTRODUCTION

The main reason for amendment 2 was to include clarity on how conversion from a-MCI to AD is measured.

26.2 AMENDMENT 2: SUMMARY OF CHANGES

Section 23.1 Secondary endpoints

Added language in bold: Conversion from a-MCI to AD **as measured by NINCDS-ADRDA criteria for diagnosis of Alzheimer Disease and Clinical Dementia Rating (CDR).**

Rationale: added language for clarity on conversion measures from a-MCI to AD.

Section 14.2.1 Conversion to AD

Added language: Conversion to AD is measured by NINCDS-ADRDA criteria for diagnosis of Alzheimer Disease and Clinical Dementia Rating (CDR) (Appendix A).

Rationale: added language for clarity on conversion measures from a-MCI to AD.

27.0 AMENDMENT 3: JUNE 2011

27.1 AMENDMENT 3: INTRODUCTION

Amendment 3 is the result of two publications in May, 2011 from the National Institute on Aging that further defined the guidelines for diagnosing pre-dementia and conversion to AD.

27.2 AMENDMENT 3: SUMMARY OF CHANGES

Underlined words have been added to the following sections.

2.3 Secondary endpoints:

Conversion from a-MCI to AD as measured by NINCDS-ADRDA, National Institute on Aging (NIA) criteria [14] for diagnosis of Alzheimer Disease, and Clinical Dementia Rating (CDR)

4.1 Inclusion criteria

3. Diagnosis of Mild Cognitive Impairment, Amnestic type (single or multi domain) according to Petersen criteria (Appendix B), NIA diagnostic guidelines, [15] and supported by a CDR score of 0.5.

14.2.1 Conversion to AD

Conversion to AD is measured by NINCDS-ADRDA and NIA [14] criteria for diagnosis of Alzheimer Disease and Clinical Dementia Rating (CDR) (Appendix A).

21.1 Schedule of study activities

a-MCI Petersen/NIA criteria review

28.0 AMENDMENT 4: DEC 2011

28.1 AMENDMENT 4: INTRODUCTION

Amendment 4 includes the addition of measurement of ventricular volume at 12 months to the secondary endpoint. Section 8.0 was included to address modifications to study activities for patients who convert to Alzheimer Disease.

28.2 AMENDMENT 4: SUMMARY OF CHANGES

2.3 Secondary endpoints:

Added language in bold: Change in ventricular volume as measured by MRI at baseline**, 12 months,** and 24 months following infusion of either 0.4 g/kg NewGam or 0.9% saline solution (placebo) every 14 days x 5 in patients with positive CSF Aβ1-42/CSF P-Tau_{181P} Alzheimer signature

Rationale: The ventricular volume changes at 12 months will be reviewed.

8.0 Conversion to Alzheimer Disease

This section was added to outline the study procedures for subjects who convert to AD and remain in the follow-up portion of the study.

Rationale: Section was added to address change in condition.

29.0 AMENDMENT 5: SUMMARY OF CHANGES

29.1 AMENDMENT 5: Introduction

The only change in this amendment consists of the extension of study follow-up from 24 months to 60 months in 12 months intervals (i.e. 24 month, 36 month, 48 month, and 60 month).

29.2 AMENDMENT 5: Rationale

The purpose of study follow-up extension is to evaluate possible efficacy over a longer duration.

Section	Original	Revised
2.0 Study Objectives	2.1 Primary Objective:	Added:

Section	Original	Revised
and Endpoints	This randomized double-blinded study will evaluate the efficacy of intravenous immunoglobulin (NewGam 10%) in patients with a-MCI over 24 months after the first infusion.	2.2 Secondary Objective: Additionally, this randomized double-blinded study will evaluate the efficacy of intravenous immunoglobulin (NewGam 10%) in patients with a-MCI over 36 months, 48 months, and 60 months after the first infusion.
2.3 Primary Endpoint	Change in ventricular volumetric as measured by MRI at baseline and 24 months following the first infusion of either 0.4 g/kg NewGam or 0.9% saline solution (placebo) every 14 days x 5.	Change in ventricular volumetric as measured by MRI at baseline, 24 months, 36 months, 48 months, and 60 months following the first infusion of either 0.4 g/kg NewGam or 0.9% saline solution (placebo) every 14 days x 5.
2.4 Secondary Endpoint	Change in ventricular volume as measured by MRI at baseline, 12 months, and 24 months following infusion of either 0.4 g/kg NewGam or 0.9% saline solution (placebo) every 14 days x 5 in patients with positive CSF Aβ1-42/CSF P-Tau$_{181P}$ Alzheimer signature Change in cognitive performance between baseline and 4, 8, 12, 16, 20, and 24 months after the first infusion as measured by:	Change in ventricular volume as measured by MRI at baseline, 12 months, 24 months, 36 months, 48 months, and 60 months following infusion of either 0.4 g/kg NewGam or 0.9% saline solution (placebo) every 14 days x 5 in patients with positive CSF Aβ1-42/CSF P-Tau$_{181P}$ Alzheimer signature Change in cognitive performance between baseline and 4, 8, 12, 16, 20, 24, 36, 48, and 60 months after the first infusion as measured by:

3.3 Estimated study duration	The duration of each study subject is approximately 24 months, including one screening visit over a period of approximately 28 days, 5 days of infusions over a 2-month period of time, and follow-up visits at 4, 8, 12, 16, 20, and 24 months after the first infusion.	The duration of each study subject is approximately 24 months, including one screening visit over a period of approximately 28 days, 5 days of infusions over a 2-month period of time, and follow-up visits at 4, 8, 12, 16, 20, and 24 months after the first infusion. Subjects will be given the option of continuing study follow-up to include 36 month, 48 month, and 60 month visits.

Section	Original	Revised
7.0 Evaluations by Visit	Visits 7 through 12 (Month 4 through Month 24) have a ±7 day window. Study completed at Visit 12, Month 24	Added: Visits 13 through 15 (Month 36 through Month 60) have a ±14 day window). Added: • Section 7.10, Visit 13, Month 36 • Section 7.11, Visit 14, Month 48 • Section 7.12, Visit 15, Month 60
8.0 Conversion to Alzheimer Disease	Depending on when the conversion occurs, the subjects will be asked to complete the following: • Complete all Visit 7 study activities described above • Complete *only the following* for Visit 8: 3. HIV-I & II, HCV, HBV, B19, HAV 4. Adverse events and Concomitant Meds • Complete all Visit 9 study activities described above • Subjects will not attend Visit 10 and Visit 11 Complete all Visit 12 study activities	Added: Complete all Visit 13, 14, and 15 study activities (optional)
12.0 Response Criteria	The MMSE, CDR-SB, and ADAS-cog are scheduled to occur at 4, 8, 12, 16, 20, and 24 months after Visit 1.	The MMSE, CDR-SB, and ADAS-cog are scheduled to occur at 4, 8, 12, 16, 20, 24, 36, 48, and 60 months after Visit 1.
15.1 Primary Endpoint	Total ventricular volume is the primary biomarker of interest. Brain MRI will be obtained at baseline and 24 months. Differences between the IVIG and placebo group at month 24 will be analyzed using analysis of covariance (ANCOVA). The	Total ventricular volume is the primary biomarker of interest. Brain MRI will be obtained at baseline, 24 months, 36 months, 48 months, and 60 months. Differences between the IVIG and placebo group at month 24, 36, 48, and 60 will be analyzed using

Section	Original	Revised
	model will include treatment as a factor with two levels (IVIG, placebo) and baseline ventricular volume as the covariate.	analysis of covariance (ANCOVA). The model will include treatment as a factor with two levels (IVIG, placebo) and baseline ventricular volume as the covariate.
15.2 Secondary endpoints	Kaplan-Meier survival curves will be estimated and will plot the proportion of treatment and control patients who remain without a diagnosis of AD at month 24. The CDR-SB, MMSE, and ADAS-cog are administered at baseline and at months 4, 8, 12, 16, 20, and 24.	Kaplan-Meier survival curves will be estimated and will plot the proportion of treatment and control patients who remain without a diagnosis of AD at month 24, 36, 48, and 60. The CDR-SB, MMSE, and ADAS-cog are administered at baseline and at months 4, 8, 12, 16, 20, 24, 36, 48, and 60.
22.1 Schedule of study activities	Describes Visits 1 through 12	Describes Visits 1 through 15 as stated above.

30.0 AMENDMENT 6: SUMMARY OF CHANGES

30.1 Introduction:

Amendment 6 consists of changes in the measurement of the primary endpoint and statistical analysis plan in sections 15.1 and 15.2

30.2 Rationale:

Since the study was designed and initiated, research from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and others have utilized a sub-classification of early MCI (EMCI) and late MCI (LMCI) to improve the understanding of effects of interventions which may be unique to particular early stages in the progression of AD. Based on those studies, and using the cognitive data available in this study, participants were classified as EMCI if baseline CDR-SB was less than or equal to 1.5 and LMCI if CDR-SB was greater than 1.5.

This amendment includes the change of primary endpoint from ventricular volume to annualized percent change in ventricular volume. The amendment also reflects the change in the statistical analysis to include early and late MCI as study factors for all endpoints.

31.0 AMENDMENT 7: SUMMARY OF CHANGES

31.1 Introduction:

Amendment 7 consists of administrative changes to the table of contents and sections 15.1 and 15.2.

31.2 Rationale:

To correct errors and add missing CSF secondary endpoint.

32.0 AMENDMENT 8: SUMMARY OF CHANGES

32.1 Introduction:

In section 15.2 we stated “Participants will also be classified as early MCI (EMCI) if baseline CDR-SB is less than 1.5, and late MCI (LMCI) if CDR-SB is greater than 1.5.” This doesn't say what happens if a patient falls at 1.5. Amendment 8 revises to state LMCI as 1.5 or greater.

32.2 Rationale:

The 1.5 cut-off more accurately depicts the early and late MCI status in that there are no conversions at year 1, and only 1 conversion at year 2 in the early MCI status.

33.0 AMENDMENT 9: SUMMARY OF CHANGES

33.1 Change:

The protocol is amended to include unblinding subjects who want to know if they received IVIG or placebo. Subjects participating in the extension portion of the study may be unblinded upon study completion. Subjects who declined participation in the extension portion of the study or who did not complete the study will be unblinded upon request.

The Principal Investigator will inform subjects of their group assignment at their last study visit, and will not have access to individual subject data following study completion.

This unblinding protocol was approved by the DSMC on 6/3/16. No changes were made to the unblinding protocol during study participation.

33.2 Rationale:

There are current and future studies for MCI and AD that exclude subjects who have had prior immunotherapy. If subjects remain blinded, placebo arm subjects will not have a chance to participate in these trials.