

**Proof of concept of the effect of Intravenous immunoglobulin on cerebral and retinal amyloid in mild cognitive impairment due to Alzheimer Disease**

**SPONSOR:** Sutter Institute for Medical Research

**PRINCIPAL INVESTIGATOR:** Shawn Kile, MD

**SPONSOR PROTOCOL#:** SIMR\_Neuro17\_SIMR\_Kile\_IVIG POC

**ORIGINAL VERSION DATE:** September 13, 2017

**AMENDMENT 1 DATE:** September 22, 2017

CONFIDENTIAL

The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless law or regulations require such disclosure. Persons to whom the information is disclosed must be informed that the

information is confidential and may not be further disclosed.

**Proof of concept of the effect of Intravenous immunoglobulin on cerebral and retinal amyloid in mild cognitive impairment due to Alzheimer Disease**

<b>1</b>	<b>SCHEDULE OF STUDY ACTIVITIES</b>	<b>4</b>
<b>2</b>	<b>BACKGROUND</b>	<b>5</b>
<b>3</b>	<b>STUDY OBJECTIVES AND ENDPOINTS</b>	<b>5</b>
3.1	Primary Objective	5
3.2	Primary Endpoints	5
<b>4</b>	<b>STUDY PLAN</b>	<b>5</b>
4.1	Study design	5
4.2	Subject population	5
4.3	Estimated study duration	6
<b>5</b>	<b>SUBJECT SELECTION</b>	<b>6</b>
5.1	Inclusion criteria	6
5.2	Exclusion criteria	6
<b>6</b>	<b>ENROLLMENT</b>	<b>8</b>
6.1	Enrollment	8
<b>7</b>	<b>STUDY DRUG AND TREATMENT</b>	<b>9</b>
7.1	Description of study drug	9
7.2	Shipping, handling, and storage	9
7.3	Special precautions for storage	9
7.4	Drug accountability	9
7.5	Study drug dosage	9
7.6	Study drug preparation and infusion	10
7.7	Incompatibilities	10
7.8	Administration	10
7.9	Rate of administration	10
7.1	Concomitant therapy	11
<b>8</b>	<b>EVALUATIONS BY VISIT</b>	<b>11</b>
8.1	VISIT 1: Screening	11
8.2	VISIT 2: Day 1 – First infusion	12
8.2.1	Study drug infusion:	12
8.2.2	Following initiation of infusion:	12
8.3	VISIT 3 (Day 14 - Second Infusion) through VISIT 6 (Day 56 - Fifth Infusion)	13
8.4	VISIT 7: Month 4 ( $\pm$ 7 days)	13
8.5	Early termination from the study	13

<b>9</b>	<b>WITHDRAWAL AND REPLACEMENT OF SUBJECTS</b> .....	<b>14</b>
9.1	Criteria for subject withdrawal.....	14
9.2	Replacement of subjects.....	14
<b>10</b>	<b>ADVERSE EVENTS</b> .....	<b>14</b>
10.1	Adverse event definition.....	14
10.2	Serious adverse event (SAE) definition.....	14
10.3	Other relevant drug safety information.....	15
10.4	Adverse event severity.....	15
10.5	Adverse event reporting.....	15
10.6	Investigator reporting to the FDA.....	16
10.7	Reporting of adverse drug reactions and other safety information.....	16
10.8	Reporting of adverse events to the institutional review board (IRB).....	16
10.9	Reporting of adverse drug reactions and other safety information to study sponsor....	16
10.10	Adverse event updates.....	17
<b>11</b>	<b>IND REPORTING</b> .....	<b>17</b>
<b>12</b>	<b>PROTOCOL DEVIATIONS</b> .....	<b>17</b>
<b>13</b>	<b>DATA RECORDING, RETENTION, AND MONITORING</b> .....	<b>17</b>
13.1	Data entry and maintenance.....	17
13.2	Study records retention.....	18
13.3	Data monitoring committee.....	18
<b>14</b>	<b>STATISTICAL ANALYSIS</b> .....	<b>18</b>
14.1	Primary endpoint.....	18
<b>15</b>	<b>SAMPLE SIZE</b> .....	<b>18</b>
<b>16</b>	<b>IMPLICATIONS AND DIRECTION FOR FUTURE STUDIES</b> .....	<b>18</b>
<b>17</b>	<b>ETHICAL AND LEGAL ISSUES</b> .....	<b>18</b>
17.1	Institutional review board approval.....	18
17.2	Informed consent.....	19
17.3	Subject confidentiality.....	19
17.4	Protocol amendments.....	19
17.5	Premature discontinuation of study.....	19
<b>18</b>	<b>REFERENCES</b> .....	<b>20</b>
<b>19</b>	<b>APPENDIX A: NINCDS-ADRDA criteria for diagnosis Alzheimer Disease<sup>8</sup></b> .....	<b>21</b>
<b>23.0</b>	<b>APPENDIX B: Clinical laboratory tests</b> .....	<b>22</b>
<b>20</b>	<b>APPENDIX C: INSTRUCTIONS FOR FLORBETAPIR PET</b> .....	<b>23</b>
<b>21</b>	<b>APPENDIX D: INSTRUCTIONS FOR RETINAL AMYLOID IMAGING</b> .....	<b>24</b>
21.1	Pupil dilation will be conducted prior to imaging.....	24

21.2 Imaging Procedure.....24  
**22 Amendment 1.....25**

**1 SCHEDULE OF STUDY ACTIVITIES**

<b>Study Visit</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>Study Time Point</b>	Day -28 To Day -1	Day 1	Day 14	Day 28	Day 42	Day 56	Month 3
<b>Visit Type (Visit Window)</b>	Screening	Infusion Visits (±1 day)					±7 days
<b>CLINICAL</b>							
Informed consent	X						
Inclusion/Exclusion	X	X					
Medical Hx/Prior/Baseline Medications	X						
NIA criteria review	X						
Modified Hachinski Ischemia Scale	X						
Vital Signs	X	X	X	X	X	X	X
Physical Exam	X	X <sup>3</sup>					X
Neurological Exam	X	X <sup>3</sup>					X
ECG	X						
Florbetapir -PET (Appendix C)	X						X
Retinal scan for amyloid (Appendix D)	X						X
Mini Mental State Exam (MMSE)	X						
CDR-SB	X						
IGA deficiency	X						
Serum viscosity	X						
CBC, Chemistry Panel (Appendix B)	X						X
TSH, Vit-B12, RPR <sup>1</sup>	X						
Urinalysis <sup>2</sup>	X						
Adverse events & Concomitant Meds		X	X	X	X	X	X
<b>THERAPY</b>							
Infusion of IVIG		X	X	X	X	X	
Assess infusion site		X	X	X	X	X	
<sup>1</sup> RPR, B12, TSH required if not done in the last 12 months prior to screening							
<sup>2</sup> Urine culture may be performed if indicated							
<sup>3</sup> May occur within 72 hours prior to first infusion							

## 2 BACKGROUND

Alzheimer's disease (AD) is a neurodegenerative disorder which causes cognitive decline and brain atrophy associated with the pathologic accumulation of amyloid and tau proteins. Passive immunization with intravenous immunoglobulin (IVIG) contains amyloid antibodies and has been investigated as a potential safe disease-modifying strategy for A $\beta$  clearance in AD.<sup>1,2</sup>

We conducted the first study investigating early administration of IVIG given in the pre-dementia stage, MCI (mild cognitive impairment), of AD. The details of this randomized, double-, placebo-controlled trial have been previously published.<sup>3</sup> Patients with MCI were randomized to receive either 0.4 g/kg of IVIG or 0.9% saline solution every 14 days x 5 infusions. The results showed that there was less brain atrophy in participants given IVIG when compared with placebo at 12 months as well as evidence of a sustained effect at 36 months based on our extension study results.

We suspect the primary mechanism of action of IVIG to be clearance of amyloid. However other possible mechanisms of IVIG have been proposed. IVIG also contains tau antibodies and has other immunomodulating properties including regulating effects on microglia which may be beneficial in modulating neuroinflammation and neurodegeneration in AD.<sup>4-7</sup>

There has never been a published study in humans using amyloid imaging to demonstrate the treatment effects of IVIG in MCI. Here we propose use of both amyloid brain PET imaging and retinal amyloid imaging (a novel surrogate scanner used to determine amyloid burden) to determine if IVIG treatment results in a measurable reduction in amyloid.

## 3 STUDY OBJECTIVES AND ENDPOINTS

### 3.1 Primary Objective

This is a proof of concept study is to determine if changes in brain amyloid levels as measured by Florbetapir PET, as well as retinal amyloid levels in the retina are evident three months after infusion of 0.4 g/kg of IVIG every 14 days x 5 infusions.

### 3.2 Primary Endpoints

Change in standard uptake values (SURV) as measured by Florbetapir PET at baseline and 3 months and Retinal Amyloid Index (RAI) as measured by amyloid levels in the retina.

## 4 STUDY PLAN

### 4.1 Study design

This is a single center, open label, proof of concept, out-patient study. Subjects will undergo Florbetapir PET and have retinal amyloid levels measured, receive an infusion of IVIG at 0.4 g/kg every 14 days for a total of five infusions, and repeat PET and retinal amyloid measures three months after the first infusion.

### 4.2 Subject population

The study population will consist of male and female subjects diagnosed with mild cognitive impairment (MCI) due to Alzheimer disease (AD).

### **4.3 Estimated study duration**

The duration of each study subject is approximately 4 months, including one screening visit over a period of approximately 28 days, 5 days of infusions over a 2-month period of time, and a follow-up visit at 3 months after the first infusion.

## **5 SUBJECT SELECTION**

### **5.1 Inclusion criteria**

1. Age 50 to <85 years.
2. Evidence of amyloid pathology on Florbetapir PET at screening.
3. Diagnosis of MCI due to AD based on NIA-AA criteria. (APPENDIX A)
4. MRI brain (with past 24 months) which shows evidence of mild hippocampal atrophy and/or bilateral parietal atrophy.
5. CDR score of 0.5
6. Mini-Mental State Examination (MMSE) score of 24-30, inclusive.
7. Rosen Modified Hachinski Ischemic score  $\leq 4$ .
8. Receiving stable doses of medication(s) for the treatment of non-excluded medical condition(s) for at least 30 days prior to screening. Cholinesterase inhibitors and memantine are allowed if doses have stable been least 30 days prior to screening.
9. Agree to refrain from participating in any treatment or clinical trial targeting amyloid for the duration of the study.
10. Agree to refrain from taking any herbal supplement considered to enhance cognition unless approved by the investigator for the duration of the study.
11. Ability to attend all clinical visits and have an informant capable of accompanying the subject on specific clinic visits.
12. The subject's collaborative informant (support person) must be someone who has known the subject for at least 4 years and has had approximately 2 or more separate communications with the study participant per month (at least one of these communications in person).
13. Fluency in English and evidence of adequate premorbid intellectual functioning.
14. Adequate manual dexterity, visual, and auditory abilities to perform all aspects of the cognitive and functional assessments.
15. Venous access suitable for repeated infusions and phlebotomy.
16. 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.

### **5.2 Exclusion criteria**

1. Has significant neurological disease other than MCI that in the opinion of the investigator 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 cm<sup>3</sup>, multiple lacunar infarcts (2 or more) or evidence of a single prior infarct > 1 cm<sup>3</sup>, 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. Sensitivity to Florbetapir.
7. Other present/planned ionized radiation that, in combination with planned exposure to PET ligands for this study, would result in cumulative exposure that would exceed recommended limits.
8. Ophthalmologic condition that would interfere with retinal amyloid imaging.
9. Current presence of a clinically significant major psychiatric disorder (e.g., Major Depressive Disorder) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) or symptom (e.g., hallucinations) that in the opinion of the investigator could affect the subject's ability to complete the study.
10. 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.
11. History of cancer within the last 5 years, with the exception of nonmetastatic basal cell carcinoma, and squamous cell carcinoma of the skin.
12. Uncontrolled hypertension (diastolic BP> 100 mmHg or systolic BP> 160 mmHg, sitting).
13. History or evidence of any clinically significant autoimmune disease or disorder of the immune system (e.g., Crohn's Disease, Rheumatoid Arthritis)
14. Clinically significant infection within the last 30 days (e.g., chronic persistent or acute infection (eg, upper respiratory infection [URI], urinary tract infection [UTI]).
15. Female subjects of childbearing potential.
16. Other clinically significant abnormality on physical, neurological, laboratory, vital signs or ECG examination (e.g., atrial fibrillation) that could compromise the study or be detrimental to the subject.
17. Weight greater than 120 kg (264 lbs).
18. Excessive smoking defined as more than 20 cigarettes per day.

19. History of alcohol or drug dependence or abuse as defined by DSM-IV criteria within the last 2 years.
20. Severe liver or kidney disease verified by the PI review of ALT, AST and creatinine.
21. Known coagulopathy, thrombosis, or low platelet count.
22. Hemoglobin less than 11 g/dL.
23. Known deficiency to IgA.
24. Positive serology for Hepatitis B or C, or HIV.
25. History of anti-amyloid treatment, immunotherapy, or other experimental treatment for MCI or Alzheimer disease.
26. Concurrent use of anticholinergic drugs including diphenhydramine.
27. Current use of anticoagulant medications (except the use of aspirin 325 mg/day or less, plavix, aggrenox, and persantine but not for stroke).
28. Concurrent use of opioid pain relievers and related synthetic derivatives.

## **6 ENROLLMENT**

Prior to the start of enrollment, all study contracts must be fully executed and 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 Institutional Review Board (SHIRB) 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).
- All applicable contracts

### **6.1 Enrollment**

A subject is considered enrolled when they have completed informed consent and received any amount of IVIG by infusion.

## **7 STUDY DRUG AND TREATMENT**

### **7.1 Description of study drug**

Octagam is an FDA approved 10% human normal immunoglobulin solution ready for intravenous administration. Adverse Drug Reactions (ADRs) reported for Octagam are expected to be similar in type and intensity to those reported with other IVIG preparations.

The Octagam 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, Octagam complies with the latest international consensus on best practices for viral safety. The Source Q chromatography (ion-exchange chromatography) step in the Octagam process also contributes significantly to the viral safety of Octagam. 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.

### **7.2 Shipping, handling, and storage**

Octagam 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 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. Octagam may be stored for 15 months at +2°C to + 8°C (36°F to 46°F) from the date of manufacture.

### **7.3 Special precautions for storage**

- Do not freeze. Frozen product should not be used
- Do not use after expiration date

### **7.4 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.

### **7.5 Study drug dosage**

The dose level of IVIG at 0.4 g/kg will be administered by IV infusion once every 14 days for two months. Subject's weight at the first infusion visit will be used for the dosing calculation for the remaining infusions. There is no provision for dose adjustments by the investigator under this protocol.

## 7.6 Study drug preparation and infusion

- The pharmacist will prepare the IVIG 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. Octagam 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 Octagam 10% is transferred into an EVA infusion bag.

## 7.7 Incompatibilities

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

## 7.8 Administration

- Octagam 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.
- Octagam 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.

## 7.9 Rate of administration

The initial infusion rate of IVIG (Octagam) 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 third 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.

### **7.1 Concomitant therapy**

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.

## **8 EVALUATIONS BY VISIT**

The overall summary of study activities by visit is provided Section 1.

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. The first dose of study drug is administered on Day 1. Visits 2 through 6 have a  $\pm 1$  day window and occur every 14 days over two months. The investigator will determine if a subject is suitable to continue following a missed infusion. Visit 7 has a  $\pm 7$  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. Prior to infusion, a review of concomitant medications and AEs takes place. If the subject continues to be eligible for enrollment, the subject will be infused with study medication and will remain in the infusion clinic for at least 1 hour following the infusion for safety assessments on Visit 2 (Day 1), and 15 minutes for the subsequent visits.

### **8.1 VISIT 1: Screening**

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

- Obtain signed and dated SHIRB 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
- NIA criteria review
- Determine Rosen Modified Hachinski Ischemic score

- Record vital signs
- Perform physical examination including height and weight
- Perform neurological examination
- Obtain standard 12-lead ECG
- Conduct MMSE and CDR assessments
- Conduct Florbetapir PET (Appendix C)
- Conduct retinal amyloid imaging (Appendix D)
- Obtain blood sample for ApoE genotyping, IgA deficiency, serum viscosity
- Obtain blood sample for complete blood count (CBC) and comprehensive metabolic panel (chemistry panel).
- Obtain blood sample for thyroid stimulating hormone (TSH), vitamin-B12 and rapid plasma reagin laboratory tests

## 8.2 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.

- 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)
- Preparation of study drug by pharmacists and deliverer to the infusion administration site.

### 8.2.1 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

### 8.2.2 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 1 hour following the completion of the infusion. The subjects may leave the clinic after the observation period if the subject is medically stable.

### **8.3 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.
- Preparation of study drug by pharmacists and deliverer to the infusion administration site.
- Administer drug as stated in 8.2.1 and 8.2.2
- 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.

### **8.4 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 blood sample for routine hematology and chemistry laboratory tests
- Conduct Florbetapir PET (Appendix C)
- Conduct retinal amyloid imaging (Appendix D)

### **8.5 Early termination from the study**

Every attempt should be made to follow each subject through the final visit 7. 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 7 or ET visit) or until the SAE has resolved or the investigator deems the event to be stable or chronic.

## 9 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 who do not complete all five infusions will be replaced.

## 10 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 7 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<sup>1</sup>
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity<sup>2</sup>
- 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 Octagam 10%, even if no adverse drug reaction occurred.

<sup>1</sup>“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.

<sup>2</sup>“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 event severity**

Severity of AEs will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 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**

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

Central Drug Safety Unit:

Email:

[cdsu@octapharma.com](mailto: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 Reporting of adverse events to the institutional review board (IRB)**

The principal investigator is required to notify the Sutter Health Institutional Review Committee (SHIRB) 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 Octagam 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 SHIRB, on file.

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

### **11 IND REPORTING**

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

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that a study completion report is provided to the FDA within 60-days of study completion. 21 CFR 312.33 provides the data elements that are to be submitted in the report. The completion 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 ([General Manager OPG / Director 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.

### **12 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 SHIRB in writing of such deviation from protocol.

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

### **13 DATA RECORDING, RETENTION, AND MONITORING**

#### **13.1 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.

### **13.2 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.

### **13.3 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.

## **14 STATISTICAL ANALYSIS**

### **14.1 Primary endpoint**

Graphs of individual changes in standard uptake ratio values (SURV) of Florbetapir PET will be compared between baseline and 3 months. Graphs of individual changes in RAI values will be compared between baseline and 3 months.

## **15 SAMPLE SIZE**

Five subjects will be included. If it appears that IVIG shows changes in these two markers, a large trial will be considered.

## **16 IMPLICATIONS AND DIRECTION FOR FUTURE STUDIES**

This study will help determine if the reason that IVIG treatment appears to reduce brain atrophy in patients with MCI is due to a reduction of CNS (central nervous system) amyloid levels.

## **17 ETHICAL AND LEGAL ISSUES**

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

### **17.1 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 SHIRB 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 SHIRB 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 SHIRB approval must be submitted by the Investigator to the SHIRB for approval. The Investigator is also responsible for notifying the SHIRB 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 SHIRB prior to use.

### **17.2 Informed consent**

Informed consent of a subject or his/her designee prior to any study related procedures must be obtained 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.

### **17.3 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.

### **17.4 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 SHIRB after consideration of Octapharma review. Written verification of SHIRB approval will be obtained before any amendment is implemented.

### **17.5 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., SHIRB/EC, regulatory authorities, etc.).

## 18 REFERENCES

1. Dodel R, Hampel H, Depboylu C, et al. Human antibodies against amyloid beta peptide: a potential treatment for Alzheimer's disease. *Annals of neurology*. Aug 2002;52(2):253-256.
2. Istrin G, Bosis E, Solomon B. Intravenous immunoglobulin enhances the clearance of fibrillar amyloid-beta peptide. *J Neurosci Res*. Aug 1 2006;84(2):434-443.
3. Kile S, Au W, Parise C, et al. IVIG treatment of mild cognitive impairment due to Alzheimer's disease: a randomised double-blinded exploratory study of the effect on brain atrophy, cognition and conversion to dementia. *Journal of neurology, neurosurgery, and psychiatry*. Sep 29 2015.
4. Negi VS, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *Journal of clinical immunology*. May 2007;27(3):233-245.
5. Boche D, Denham N, Holmes C, Nicoll JA. Neuropathology after active Aβ<sub>42</sub> immunotherapy: implications for Alzheimer's disease pathogenesis. *Acta neuropathologica*. Sep 2010;120(3):369-384.
6. Magga J, Puli L, Pihlaja R, et al. Human intravenous immunoglobulin provides protection against Aβ<sub>42</sub> toxicity by multiple mechanisms in a mouse model of Alzheimer's disease. *J Neuroinflammation*. 2010;7:90.
7. Smith LM, Coffey MP, Klaver AC, Loeffler DA. Intravenous immunoglobulin products contain specific antibodies to recombinant human tau protein. *International immunopharmacology*. Aug 2013;16(4):424-428.
8. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. Jul 1984;34(7):939-944.

**19 APPENDIX A: NINCDS-ADRDA criteria for diagnosis Alzheimer Disease <sup>8</sup>**

- 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

*20.0.1     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

*20.0.2     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

*20.0.3     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
- 20.0.4 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.

**23.0 APPENDIX B: Clinical laboratory tests**

<b>Comprehensive Metabolic Panel</b>	<b>Complete Blood Count with differential</b>	<b>Urinalysis</b>
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	

**20 APPENDIX C: INSTRUCTIONS FOR FLORBETAPIR PET**

Imaging will be acquired on a Siemens Biograph mCT (Ultra High-Definition PET/40 slice CT) scanner. Dosing will be 10 mCi Florbetapir in a peripheral vein with saline flush. A 10-minute acquisition will be obtained 30 to 50 minutes after administration. Image data will be processed by iterative reconstruction with all corrections (TOF, PSF modeling, scatter) 256 matrix, 2X zoom, 2.0 Gaussian filter. Images will be interpreted by a radiologist/nuclear medicine physician trained to read Florbetapir studies. Patients with positive studies (moderate to frequent beta amyloid neuritic plaques) will be included in the study and will undergo a repeat Florbetapir PET/CT brain imaging study 3 months later after treatment with either IVIG or placebo.

Analysis: Florbetapir is normally washed out of the cerebellar cortical gray matter in both healthy controls (HC) and in Alzheimer's dementia patients (AD). As such, it is used as the reference region for SUVR calculation. Regions of interest will be drawn around areas of cerebral gray matter in the frontal, lateral temporal, parietal and parieto-occipital regions using the fused PET/CT images and SUVRs will be calculated using the ratio of these SUV values to the value in the cerebellar gray standard uptake value.

## 21 APPENDIX D: INSTRUCTIONS FOR RETINAL AMYLOID IMAGING

NeuroVision Imaging, LLC is providing the equipment and software analysis for retinal amyloid imaging.

### 21.1 Pupil dilation will be conducted prior to imaging.

Administer:

1. Proparacaine 0.5% - numbing – 1 drop OU -wait 2 minutes
2. Tropicamide 0.5% (Mydracil) –1 drop OU– wait 3 minutes
3. Phenylephrine HCl 2.5% - 1 drop OU – wait until dilated >3.5 mm

### 21.2 Imaging Procedure

The imaging shall use the Retia device with software version 1.4.5 or later.

For each study scan, capture autofluorescence images of the Superior field in 3 focal plans, up to 6 images each

#### a. Image set 1 of 3

- i. First image – Full automatic IR and AFL of superior field.
- ii. Images 2 to up to 6

1. Review the fully automatic IR image and read/record the machine diopter set point (to the tenths digit, e.g. 2.4)

2. Start a new exam, select Superior, and then go to Manual Alignment and Focus mode

a. Use the slider and joystick buttons to enter the previously recorded autofocus value to the nearest tenth of an MD.

b. Use the on-screen buttons and take one IR and then the sequence of 5 AFL images (one every 5 -10 seconds, the LED cycle time).

#### b. Image set 2 of 3

i. Without exiting the exam,

ii. Move the focus point -2 MD using the slider and/or the joystick buttons (e.g. if the initial focus point was 2.4, then move the focus point to 0.4).

iii. Use the on-screen buttons to take one IR and then the sequence of up to 6 AFL images, one every 5 or so seconds.

#### c. Image set 3 of 3

i. Without exiting the exam,

ii. Move the focus point +4 MD (+2 MD from the original recorded focus point, 4.4 in our example here) using the slider and/or the joystick buttons.

iii. Use the on-screen buttons to take one IR and then the sequence of up to 6 AFL images.

## **22 Amendment 1**

- NewGam 10% changed to Octagam 10%