2. SYNOPSIS

Name of Sponsor/Company: Baxter Healthcare Corporation Baxter Innovations GmbH		*(For National Authority Use only)*
Name of Investigational Product (IP)	GAMMAGARD LIQUID	
Name(s) of Active Ingredient(s)	Immune Globulin Intravenous (Human), 10% (IGIV, 10%)	
CLINICAL CONDITION(S)/INDICATION(S)		
• Alzheimer's disease (AD)		
PROTOCOL IDENTIFIER	161003	
PROTOCOL TITLE	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Effectiveness of Immune Globulin Intravenous (Human), 10% (IGIV, 10%) for the Treatment of Mild to Moderate Alzheimer's Disease (AD)	
Short Title	Phase 3 IGIV, 10% in AD	
STUDY PHASE	Phase 3	
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PUBLICATION (REFERENCE): None

STUDY PERIOD

Initiation	2012 JAN 23
Study Completion	2013 JUL 16
Duration	18 months

STUDY OBJECTIVES AND PURPOSE

Study Purpose

The purpose of this study was to provide evidence of efficacy and safety to support the development of IGIV, 10% as a treatment option for patients with mild to moderate AD.

Primary Objective

- To evaluate the efficacy of IGIV, 10% treatment on change in cognitive performance and functional activities in subjects with mild to moderate AD, as compared to placebo.

Secondary Objective(s)

- To evaluate the effects of IGIV, 10% treatment on additional outcomes, including global clinical status, neuropsychiatric behaviors, and changes in volumetric magnetic resonance imaging (MRI) parameters.
- To examine the effects of IGIV, 10% treatment on disease-specific quality of life of subjects with mild to moderate AD and of their caregivers.
- To assess the safety of IGIV, 10% treatment in subjects with mild to moderate AD.

STUDY DESIGN

Study Type/ Classification/ Discipline	Efficacy, Safety
Control Type	Placebo
Study Indication Type	Treatment
Intervention model	Parallel Assignment
Blinding/Masking	Double-Blind

Study Design	This was a Phase 3, prospective, randomized, double-blind, placebo-controlled, multicenter, global study to evaluate the safety and effectiveness of 2 doses of IGIV, 10% (200 or 400 mg/kg body weight [BW] every 2 weeks) compared with placebo (human albumin 0.25%) as an add-on pharmacotherapy for the treatment of mild to moderate AD. This study was planned to include approximately 402 randomized subjects with Probable AD who were in mild to moderate stages of disease severity. At screening, to establish eligibility for participation in the study, subjects' diagnosis and disease severity was to be assessed, and physical, neurological and laboratory assessments were to be performed. Subjects meeting eligibility criteria and successfully completing baseline assessments were to be randomized in a 1:1:1 ratio to receive either of two doses of IGIV, 10% or placebo every 2 weeks, in a double-blind fashion over a period of 18 months. In order for the infusion volumes of the two IGIV, 10% doses to be the same, IGIV, 10% was to be diluted with 5% dextrose in water (D5W) for the 200 mg/kg BW dose so that the infusion volume of each IGIV, 10% dose was 4 mL/kg BW. Placebo was to be administered at an infusion volume of 4 mL/kg BW to match the equivalent infusion volume of the two IGIV, 10% doses. Infusions were required to be administered by a qualified healthcare professional. A minimum of the initial 3 infusions were to be administered at the study site or infusion center. At the investigator's discretion, the remaining infusions were allowed to be administered at the study site, infusion center or at the subject's home or other suitable location, as acceptable per local regulations and standard practices of the study site. Subjects were to undergo follow-up assessments including cognitive, functional, global clinical status, and neuropsychiatric measures at 3-month intervals until the Month 18 follow-up visit. Quality of life follow-up assessments were to be performed at the Month 6, Month 9, Month 12 and Month 18 follow-up visits. Volumetric MRI, physical and neurological exams, safety laboratory tests, and pharmacoeconomic assessments were to be performed at the Month 9 and Month 18 follow-up visits. In a subset of study sites, subjects were allowed participate in a neuroimaging sub-study using 2-fluorodeoxyglucose (FDG)-positron emission tomography (PET). The target accrual for the FDG-PET sub-study was 120 subjects (with a target of 40 subjects in each treatment group). FDG-PET scans were to be performed at baseline and at the Month 9 and Month 18 follow-up assessment visits. Based on results from the 18-month Phase 3 clinical study of IGIV, 10% in mild to moderate AD (Baxter study 160701), sample size adjustments and/or reduction of a dose arm were allowed to be made during the course of this study (study 161003) accounting for the treatment effect size observed in study 160701.

	This study was terminated by Baxter after it was announced on 2013 MAY 07 that the earlier Phase 3 study (160701) did not meet its co-primary outcome measures of change from baseline at 18 months in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) and Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory (ADCS-ADL).

CRITERIA FOR EVALUATION

Efficacy:

Co-primary Efficacy Outcomes:

- ADAS-Cog at 18 months
- ADCS-ADL at 18 months

Secondary Efficacy Outcomes:

- ADCS-Clinical Global Impression of Change (CGIC) at 18 months
- Neuropsychiatric Inventory (NPI) at 18 months
- Logsdon Quality of Life in Alzheimer's Disease (QOL-AD)
- Impact of Alzheimer's Disease on Caregiver Questionnaire (IADCQ)
- Rate of whole brain atrophy and ventricular enlargement using volumetric MRI at 18 months

Safety:

- Number (percentage) of subjects experiencing related adverse events (AEs) and/or serious adverse events (SAEs)
- Number (percentage) of subjects experiencing any AEs and/or SAEs
- Number (percentage) of infusions temporally associated (defined as during or within 72 hours of completion of an infusion) with AEs and/or SAEs
- Number (percentage) of infusions associated with AEs and/or SAEs occurring during or within 7 days of completion of an infusion
- Number (percentage) of infusions causally associated with AEs and/or SAEs
- Number and proportion of infusions discontinued, slowed, or interrupted due to an AE

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION, AND BATCH NUMBER

Investigational Product(s)	IGIV, 10% **Dosage form**: Injection, solution **Dosage frequency**: Every 2 weeks (± 7 calendar days) **Doses**: -200 mg/kg BW/2 weeks and 400 mg/kg BW/2 weeks **Mode of Administration:** Intravenous **Batch number(s):** LE12M130AE, LE12M151AC, LE12M323AB, LE12M239AH, LE12M239AM, LE12N005AB, LE12L205AC, LE12K354AC, LE12K202AD, LE12K153AF, LE12K205AF, LE12L179AC, LE121J19AB, LE12MA19AB
Placebo/ Control	Human albumin 0.25% **Dosage form**: Injection, solution **Dosage frequency**: Every 2 weeks (± 7 calendar days) **Doses**: 4 mL/kg BW/2 weeks **Mode of Administration:** Intravenous **Batch number(s):** VNA1K129, LA11D100AA, LA12D092AA, VNA1L137

Duration of treatment:	Planned: 18 months Actual: Variable per subject due to early study termination
SUBJECT SELECTION	
Planned	Approximately 402 randomized subjects
Analyzed	ITT dataset: 232 randomized subjects PP dataset: 57 randomized subjects (for whom the Month 9 ADAS Cog and ADCS ADL assessments were available, and who received all or part of at least 90% of protocol prescribed infusions, i.e. at least 16 infusions until the Month 9 visit). A-PP dataset: The number of randomized subjects, who received all or part of at least 90% of protocol-prescribed infusion and for whom both baseline and final biomarker measurements were available and valid (the A-PP dataset), was as follows: o Ventricular volume – 41 subjects o Brain volume – 33 subjects o Hippocampal volume – 39 subjects o Left entorhinal cortex volume – 48 subjects o Right entorhinal cortex volume – 48 subjects

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Inclusion Criteria

1. Males or females of age 50 to 89 years inclusive at the time of screening
2. Diagnosis of Probable AD according to National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) 1984 criteria
3. Dementia of mild to moderate severity (MMSE 16-26 inclusive at the time of screening)
4. Stable doses of AD medication (acetylcholinesterase inhibitor and/or memantine) for at least 12 weeks prior to screening; subjects must not be on two acetycholinesterase inhibitors concurrently
5. If receiving psychoactive medications, on stable doses for at least 6 weeks prior to screening
6. For subjects with a coronary artery stent, documented medical clearance of no increased risk for stent occlusion with immunoglobulin treatment
7. For subjects with an endovascular stent, documented medical clearance of no increased risk for thromboembolic events with immunoglobulin treatment

Exclusion Criteria

1. Possible AD (per NINCDS-ADRDA criteria) or non-Alzheimer dementia (eg, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, or dementia arising from other diseases or conditions such as Parkinson's disease, vitamin B12 deficiency, thyroid abnormalities).
2. Current residence in a skilled nursing facility.
3. Contraindication to undergoing MRI (eg pacemaker [with the exception of an MRI-compatible pacemaker], severe claustrophobia, ferromagnetic implants such as a metal plate).
4. Clinically significant congestive heart failure (e.g. New York Heart Association [NYHA] Class III/IV symptoms or untreated Class II).

5. Current atrial fibrillation of unstable angina (angina at rest) or history of myocardial infarction within the 12 months prior to screening.
6. Uncontrolled hypertension defined as systolic blood pressure > 160 mm Hg and/or diastolic > 100 mm Hg confirmed upon repeated measures.
7. History of thrombosis and/or thromboembolic disease (central or peripheral) within the 12 months prior to screening.
8. Known history of procoagulant abnormalities (e.g. factor V Leiden, antiphospholipid syndrome, protein S/protein C deficiency, AT III deficiency).
9. History of intracerebral hemorrhage within the 5 years prior to screening.
10. Evidence on MRI of: greater than 4 microhemorrhages (regardless of their anatomical location or diagnostic characterization as "possible" or "definite"), a single area of superficial siderosis, vasogenic edema, a macrohemorrhage, major stroke, prominent white matter disease with a rating score of 3 on the age-related white matter changes (ARWMC) scale from the European Task Force on ARWMC,[i] or multiple lacunae (defined as more than 2 lacunae that are greater than 0.5 mm[ii] in size).
11. Head trauma with loss of consciousness, contusion, or open head injury within the 12 months prior to screening.
12. Uncontrolled seizure disorder as defined by two or more breakthrough seizures per year despite adequate antiepileptic drug (AED) treatment.
13. Modified Hachinski score > 4 at time of screening.
14. Subjects with active malignancy or history of malignancy within 5 years prior to screening with the exception of the following: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and stable prostate cancer not requiring treatment.
15. Active autoimmune or neuro-immunologic disorder.
16. Uncontrolled major depression, psychosis, or other major psychiatric disorder(s).
17. Poorly controlled diabetes, defined as glycosylated (or glycated) hemoglobin (HbA1c) ≥ 6.5% at screening.
18. Creatinine clearance < 50% of normal adjusted for age and gender, as calculated according to the Cockcroft-Gault formula,[iii] at the time of screening.[iv]
19. Known history of untreated vitamin B12 deficiency within 6 months prior to screening, or clinically significant abnormally low vitamin B12 at the time of screening.

[i] Wahlund LO, Barkhof F, Fazekas F et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32: 1318-1322.

[ii] A typographical error was noted in Protocol Amendment 3 (lacunae should have been > 5 mm in size, not greater than 0.5 mm). Protocol Amendment 4 was immediately developed to correct the error, but it never executed because the study was terminated. The medical director was involved in reviewing the results of all admission MRIs based on the correct inclusion/ exclusion criteria.

[iii] Formula:

For males: $$CL_{Cr} = \frac{(140 - Age\ [in\ years]) \times Body\ weight\ (in\ kg)}{72 \times Serum\ creatinine\ (in\ mg\ /\ dL)}$$

For females: $$CL_{Cr} = \frac{(140 - Age\ [in\ years]) \times Body\ weight\ (in\ kg) \times 0.85}{72 \times Serum\ creatinine\ (in\ mg\ /\ dL)}$$

[iv] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16: 31-41.

20. Abnormal clinical chemistry panel or hematology panel meeting any one of the following criteria:
    a. Serum alanine aminotransferase (ALT) > 2.5 x upper limit of normal (ULN)
    b. Clinically significant anemia that precludes repeated blood sampling or hemoglobin (Hgb) < 10.0 g/dL
    c. Absolute neutrophil count (ANC) < 1000 cells/µL
    d. Known coagulopathy or platelet counts < 100,000 cells/µL
    e. Total serum protein > 9 g/dL
21. Known history of or positive serology at screening for one or more of the following: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) type 1/2 antibody.
22. Immunoglobulin A (IgA) deficiency (< 8 mg/dL).
23. Known history of hypersensitivity following infusions of human blood or blood components (e.g. human immunoglobulins or human albumin).
24. Currently receiving or has received: anti-CD20 therapy within 12 months prior to screening, or other immunomodulatory therapies (eg, anti-TNF, anti-IL-1, interferon) within 12 weeks prior to screening. The following exceptions are allowed : non-systemic corticosteroids (eg, topical, opthalmic or inhaled glucocorticoids) and low-dose systemic corticosteroids (prednisone < 10 mg/day or its equivalent).
25. Currently receiving or has received intravenous or subcutaneous immunoglobulin treatment within the 2 years prior to screening, or has received immunoglobulin in Baxter Protocol 160701.
26. Currently receiving or has received at any time active immunization aimed at modulating AD progression.
27. Currently receiving or has received within 12 months prior to screening any investigational device, drug or biologic (eg passive immunotherapies with monoclonal or polyclonal antibodies) aimed at modulating AD progression.
28. Subject has been exposed to an IP or investigational device (not covered under Exclusion Criteria #26 or #27) within 12 weeks prior to screening or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
29. Subject is a family member or employee of the investigator.
30. The subject is nursing or intends to begin nursing during the course of the study.
31. Any disorder or disease, or clinically significant abnormality on laboratory or other clinical test(s) (e.g. blood tests, urine tests, electrocardiogram, chest x-ray), that in medical judgment may impede the subject's participation in the study, pose increased risk to the subject, or confound the results of the study.
32. Currently receiving anti-coagulant agent and/or anti-platelet agent other than acetylsalicylic acid (a.k.a. aspirin).

STATISTICAL METHODS

Analysis Populations

- Intent-to-Treat (ITT): All randomized subjects
- Per Protocol (PP): All randomized subjects who received all or part of at least 90% of protocol-prescribed infusions and for whom final ADAS-Cog and ADCS-ADL assessments were available

- Available Per Protocol (A-PP; used for analysis of biomarker and imaging parameters): Defined for each biomarker as "all randomized subjects who received all or part of at least 90% of protocol-prescribed infusion and for whom both baseline and final biomarker measurements were available and valid."
- Safety Set: All subjects exposed to study product (active or placebo)

Primary Efficacy Analysis (ITT dataset)

The two co-primary endpoints were assessed separately, within a repeated-measure mixed model framework, accounting for the fixed effects of treatment, visit and ApoE-ε4 carrier status (carrier/non-carrier) as class variables. Age and education level (both in years) at baseline and baseline ADAS-Cog (or ADCS-ADL, respectively) were included in the model as continuous covariates. Subjects who withdrew or were lost to follow-up were analyzed by the linear mixed model and scores of missing evaluations were not imputed. No adjustment for the type 1 error rate was needed, as this was a hierarchical, closed testing procedure. As a sensitivity analysis, the mixed model was also fitted for subjects in the PP dataset.

Secondary Efficacy Analysis

ADCS-CGIC, NPI, and QOL-AD were analyzed on the ITT dataset using mixed model analyses similar to the one used for the primary efficacy analysis. Descriptive statistics were provided for the IADCQ, also based on the ITT dataset. For the volumetric MRI measurements, an analysis of covariance (ANCOVA) model was applied to the A-PP dataset, with change from baseline at 9 months as the dependent variable and treatment group, ApoE-ε4 carrier status, and MRI baseline measurements as the explanatory variables. An exploratory repeated correlation analysis between volumetric MRI measurements and ADAS-Cog scores was also performed.

Sample Size Calculation

The planned sample size was calculated to provide 97% power to detect a mean difference of 6 points in ADAS-Cog and a mean difference of 5 points in ADCS-ADL between the 400 mg/kg BW IGIV, 10% group and the placebo group, at a 5% significance level.

SUMMARY – CONCLUSIONS

Efficacy Results:
Co-primary Efficacy Outcomes: No subject reached 18 months of treatment prior to the study termination; therefore, the pre-planned analysis of 232 ITT subjects was not performed. An exploratory ITT analysis of data with time-points up to and including the Month 9 visit was conducted, and an exploratory PP analysis of the 57 subjects who had efficacy assessments at Month 9 and who received 90% of their infusions was conducted. The ITT and PP analysis comparing the change of the co-primary efficacy outcome measures cognitive decline (ADAS-Cog) and functional abilities (ADCS-ADL) in IGIV, 10%-treated (400 mg/kg and 200 mg/kg) and placebo-treated subjects were not statistically significant. The mean (SD) observed change from baseline to Month 9 in ADAS-Cog score was 4.0 (6.44) in the 400 mg/kg treatment arm, 4.4 (8.56) in the 200 mg/kg treatment arm, and 3.1 (4.28) in the placebo arm. For the ADCS-ADL assessment, the mean (SD) observed change was -8.1 (7.36) in the 400 mg/kg treatment arm, -5.0 (11.64) in the 200 mg/kg treatment arm, and -3.8 (9.26) in the placebo arm.

Secondary Efficacy Outcome(s): No statistically significant improvements were noted in any of the secondary efficacy outcome measures, including other measures of cognitive function; clinical, behavioral, and functional assessments; and pharmacoeconomic assessments.

Safety Results:
Subjects in all arms of the study received infusions every 2 weeks until the early the early termination of the study. The median duration of the study was 141.0 days per subject in the IGIV, 10% arms (138.0 days in the 400 mg/kg arm and 160.0 days in the 200 mg/kg arm) and 183.0 days in the placebo arm, during which a median of 8, 10, and 12 infusions were administered per subject in the IGIV, 10% 400 mg/kg, IGIV, 10% 200 mg/kg, and placebo arms, respectively.

Safety Outcomes:
Overall, 160/251 (63.7%) subjects reported 570 AEs; 27 events in 19/ 251 (7.6%) subjects were serious and 543 in 156/251 (62.2%) subjects were non-serious. There were 181 product-related non-serious AEs in 71/251 (28.3%) subjects and 5 product-related SAEs in 2/251 (0.8%) subjects. One subject each in the 400 mg/kg arm and placebo arm reported product-related SAEs. More subjects treated with IGIV, 10% experienced non-serious product-related AEs compared to placebo: 30 (36.1%), 25 (29.4%), and 16 (19.3%) subjects in the 400 mg/kg, 200 mg/kg, and placebo arms, respectively. Similarly, more IGIV, 10% infusions were causally associated with AEs (or SAEs) compared to placebo infusions (94/1752 [5.4%] IGIV, 10% infusions and 30/1023 [2.9%] placebo infusions) and more IGIV, 10% infusions were discontinued, slowed, or interrupted due to an AE compared to placebo infusions (9/1752 [0.5%] IGIV, 10% infusions and 1/1023 [0.1%] placebo infusions).

There were no deaths reported during the study. One death was reported after study termination, nearly 6 months after the last 200 mg/kg IGIV, 10% treatment; the death was the result of a gastrointestinal bleed, acute blood loss and sepsis which was considered unrelated to study product.

Adverse drug reactions (ADRs) were defined as adverse events that began during infusion or within 72 hours of completion of infusion regardless of causality or related AEs regardless of time. Of 2,775 infusions administered during the study, 5 (0.2%) infusions (4/1752 [0.2%] in the combined IGIV, 10% treatment groups and 1/1023 [1.6%] in the placebo arm) were associated with serious ADRs (urinary tract infection, angina pectoris, encephalopathy, fall, headache, hemiparesis, mental status changes in IGIV, 10%-treated arms). Two hundred twenty-six (8.1%) infusions were associated with non-serious ADRs. The most common non-serious ADR was headache (29 infusions in 19 subjects in the IGIV, 10%-treated arms and 5 infusions in 5 subjects in the placebo-treated arm). Other non-serious ADRs occurring in >5% of subjects treated with IGIV, 10% were fatigue (7.1%), infusion site extravasation (6.5%), rash (6.5%), back pain (6%), and nausea (5.4%).

There was not a statistically significant increase in risk with IGIV, 10% treatment compared to placebo for any non-serious AE.

The following known, labeled risks of IGIV, 10% were assessed:

- Allergic/hypersensitivity responses including anaphylaxis and hemolysis
  - No cases of anaphylaxis occurred during this study.
  - More subjects in the IGIV, 10% arms than in the placebo arm experienced significant rashes: 15 (18.1%), 12 (14.1%), and 2 (2.4%) subjects in the 400 mg/kg, 200 mg/kg, and placebo arms, respectively.
  - Other symptoms of allergic reactions were also examined. Most subjects who experienced an AE of chills were in the IGIV, 10% arms (7/168 [4.2%]) as compared to the placebo arm (1/83 [1.2%]). Pyrexia (3/168 [1.8%] subjects) and eosinophilia (1/168 [0.6%] subjects) were reported in the IGIV, 10% arms; there were no reports of basophilia.
  - Three (1.8%) subjects, all in the 200 mg/kg arm, experienced a notable decrease in hemoglobin (>2.0 g/dL) between consecutive visits and 6 IGIV, 10%-treated subjects experienced a decrease in hemoglobin >1.5 g/dL between consecutive visits. None of the subjects receiving placebo had decreases in hemoglobin. The mechanism for decrease in hemoglobin in the IGIV, 10% arm could not be identified.
- TRALI: No respiratory failures occurred during the study.

- Renal failure: Subjects treated with IGIV, 10% did not demonstrate an increased risk of renal failure. During the study, 1 subject who had a history of renal disease in the 200 mg/kg IGIV, 10% arm experienced new or worsening renal failure.
- Thrombotic and thromboembolic events: Three venous embolic and thrombotic and thrombophlebitis and 1 arterial, vessel type unspecified, or mixed arterial and venous embolic and thrombotic events occurred during or after treatment with IGIV, 10% (1 additional event occurred during or after placebo treatment).

MRI was used for the dual purposes of clinical safety assessment and volumetric measurements. The majority of subjects did not have additional microhemorrhages compared to baseline.

An SAE of acute encephalopathy, possibly related, was reported approximately 22 hours after an infusion in 1 subject in the 400 mg/kg IGIV, 10% arm. This event resolved and the subject recovered. Posterior reversible encephalopathy syndrome has been reported as a rare event following IGIV therapy.

Fewer subjects reported infections in the IGIV, 10% arms than in the placebo arm (15.5% vs. 18.1%).

Conclusion:

The exploratory analysis of the subjects who had 9 months of efficacy data for the co-primary efficacy outcome measures of reducing cognitive decline (ADAS-Cog) and preserving functional abilities (ADCS–ADL) did not reveal any statistically significant differences between treatments. Treatment with IGIV, 10% in a population with AD of mild to moderate severity was well tolerated and no new safety signal was identified. Overall, the safety data from this study adds to the safety information available from the earlier study 160701. In conclusion, the results of Baxter clinical study 161003 extend an already established record of safety for the use of IGIV, 10% to subjects aged 51 to 88 years of age.

Date of Report: 2014 JUN 17