

A Randomized Double Blind
Placebo Controlled Study of
IVIg in Patients with Voltage
Gated Potassium Channel
Complex Antibody Associated
Autoimmune Epilepsy

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***A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED STUDY
OF IVIG IN PATIENTS WITH VOLTAGE GATED POTASSIUM
CHANNEL COMPLEX ANTIBODY ASSOCIATED AUTOIMMUNE
EPILEPSY.***

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
IVIG	Intravenous immune globulin

Study Summary

Title	<i>A randomized double blind placebo controlled study of IVIG in patients with voltage gated potassium channel complex antibody associated autoimmune epilepsy.</i>
Running Title	<i>IVIG treatment in VGKC associated autoimmune epilepsy study</i>
Protocol Number	<i>IRB#15-005649</i>
Phase	<i>Phase III/IV</i>
Methodology	<i>Study design type, such as single blind, double blind or open label; Randomized, placebo or active placebo control; cross-over design, etc.</i>
Overall Study Duration	<i>2 years</i>
Subject Participation Duration	<i>15 months</i>
Single or Multi-Site	<i>Single Site.</i>
Objectives	<i>To assess in a blinded randomized controlled fashion, whether 5 weeks of IVIG can reduce or stop seizures in patients with VGKC Ab associated autoimmune epilepsy.</i> <i>To evaluate the safety and tolerability of IVIG in VGKC Ab associated autoimmune epilepsy</i>
Number of Subjects	<i>30 Subjects</i>
Diagnosis and Main Inclusion Criteria	<i>A diagnosis of autoimmune epilepsy with ≥ 2 seizures per week and seropositivity for VGKC complex antibodies (value $>0.1nM$; normal $\leq 0.02nM$) or positive for LGII/CASPR2 Ab by CBA.</i>
Study Product, Dose, Route, Regimen	<i>Gamunex-C (Immune Globulin IV (Human)) or Placebo, IV infusion of. 0.5g/kg dose one, 1g/kg dose two, 0.6g/kg dose three, 0.6g/kg dose four.</i>
Duration of Administration	<i>5 weeks for IVIG Groups, 12 weeks for placebo crossover</i>
Reference therapy	<i>Placebo</i>
Statistical Methodology	<i>Primary outcome, which is binary variable, i.e. proportion of patients responding to treatment (yes, no) will be estimated along with 95% exact binomial confidence intervals for each arm of the respective study. These proportions will then be compared using Fisher's exact test within the study. Continuous outcomes of interest will be compared using two sample t-test or Wilcoxon rank sum test as appropriate.</i>

1 Introduction

This study evaluates the utility of IVIG in the evaluation and management of patients with suspected autoimmune epilepsy associated with voltage gated potassium channel complex autoantibodies (VGKC Ab).

The described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations, and all applicable institutional research requirements.

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Approximately one-third of epilepsy cases are intractable to antiepileptic drug (AED) therapy.¹ Seizures are recognized as a common manifestation of autoimmune limbic encephalitis and multifocal paraneoplastic disorders often encountered in the hospital or ICU setting.²⁻⁷ Accumulating evidence supports an autoimmune basis for seizures in the absence of syndromic manifestations of limbic encephalitis for a subset of AED-resistant epilepsy.^{8,9} In fact, a recent population level study, performed at Harvard Medical School, reported that the risk of epilepsy was significantly increased among patients with autoimmune diseases (odds ratio, 3.8).¹⁰

A substantial proportion of autoimmune epilepsy is associated with autoantibodies directed against the extracellular domains of cell-surface proteins which are critical in the regulation of neuronal excitability.⁸ These include voltage gated potassium channel complexes [VGKC: LGI1, CASPR2],^{11,12} voltage gated calcium channels [VGCC: PQ and N type]^{8,9} and a variety of neural receptors including the NMDA, GABA,¹³ and ganglionic acetyl choline receptor⁹ among others. Our laboratory is identifying large numbers of patients annually with these neural autoantibodies (including ~2000 with VGKC Abs, 1500 with gAChR Abs, 800 with VGCC Abs [Pittock, unpublished data]). The clinical importance of autoimmune epilepsy lies in their frequent immunotherapy-response and, less commonly, their association with distinctive tumors. It is critically important to recognize treatable and potentially reversible autoimmune epilepsy in neurological practice. It is important to note that the vast majority of patients with autoimmune epilepsy are attending outpatient neurology clinics (the focus for this study) and are not, as some may think, being managed exclusively in the inpatient/ICU setting. There are no current controlled trials for choice of agent or length of treatment and insurance companies increasingly deny coverage of certain treatments, particularly IVIG. It is thus imperative that trials be conducted to prove efficacy.^{9,14} In a recent editorial by Stephan Ruegg and Jessica A. Panzer¹⁴ regarding Toledano's paper "Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy",⁹ they stated "These results lay the needed foundation for a randomized controlled trial of Immune therapy in presumed autoimmune epilepsy, which would compare standardized treatment groups, thereby eliminating biases with regards to treatment choice and disease severity". This study should also pave the way for additional prospective studies regarding the natural history of autoimmune pharmacoresistant epilepsy and serves to raise awareness of the role of immunotherapy in the treatment of refractory epilepsies.

Clinical clues which have historically helped clinicians identify patients with autoimmune encephalopathies are outlined in Figure 1.⁹ These serve the basis for this study's inclusion criteria.

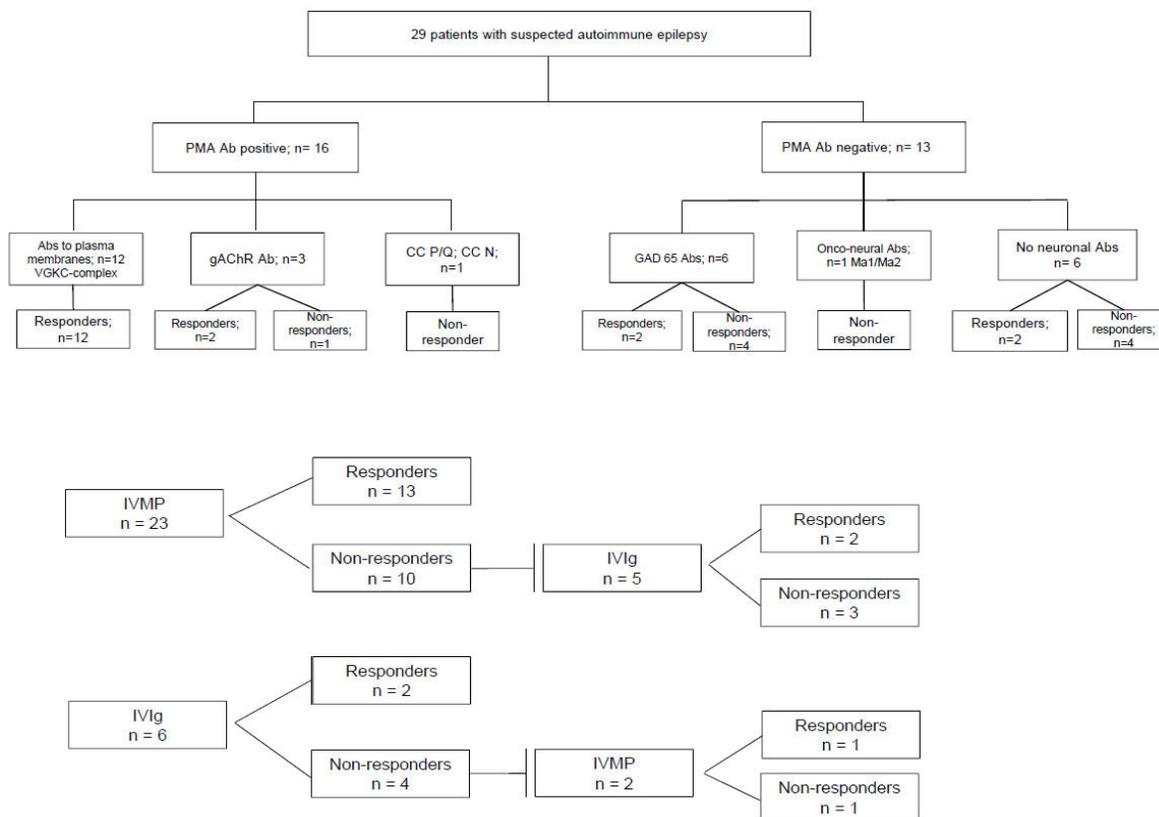
Figure 1. Clinical features suspicious for an autoimmune epilepsy.

Autoimmune Epilepsy

- Subacute onset
- Fluctuating course
- Multiple seizure types or Faciobrachial dystonic seizures
- AED Resistance
- Personal or family history (1st degree relative) of autoimmunity
- History of recent or past Neoplasia
- Evidence of CNS inflammation on CSF (elevated protein, pleocytosis, oligoclonal bands, + CSF index)
- Evidence of CNS inflammation on MRI (mesial temporal or other regional T2 hyperintensity)
- Hypometabolism/hypermotabolism on functional/PET imaging
- Detection of neural autoantibody

IVIg in autoimmune epilepsy: Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy. We recently performed a retrospective review of 29 patients treated with 6-12 weeks of intravenous methylprednisolone or immune globulin, or both (the current standard immunotherapy trial protocol used at Mayo Clinic), for suspected autoimmune epilepsy.⁹ Similar to AED trials, treated patients were considered “responders” if there was a 50% or greater reduction in seizure frequency. A total of 18 patients (62%) responded favorably to the immunotherapy trial (Figure 2). Ten of these (56%) achieved seizure freedom and the remainder had more than 50% reduction in seizure frequency. Five of eleven responders with daily seizures (45%) became seizure free after completion of the immunotherapy trial, 45% had only monthly seizures and 1/11 (9%) had weekly seizures. Two out of 4 responders with weekly seizures (50%) became seizure free and the other two had monthly seizures. All three responders with monthly seizures became seizure free. None of the responders who had generalized tonic-clonic seizures at presentation (8/18; 44%) continued having these after completion of the trial. Fifteen patients (52%) responded to the first agent tried and 14 (48%) did not. Having failed the first agent, 3 of 7 patients (43%) responded to a second agent (Figure 2). Of the fifteen patients who improved with the first immunotherapy trial, 6 responded within the first week, 6 responded in the second to fourth weeks and one required treatment for 5 weeks before improvement was noted.

Figure 2. Flow-chart of "immunotherapy trial" and response according to antibody type.



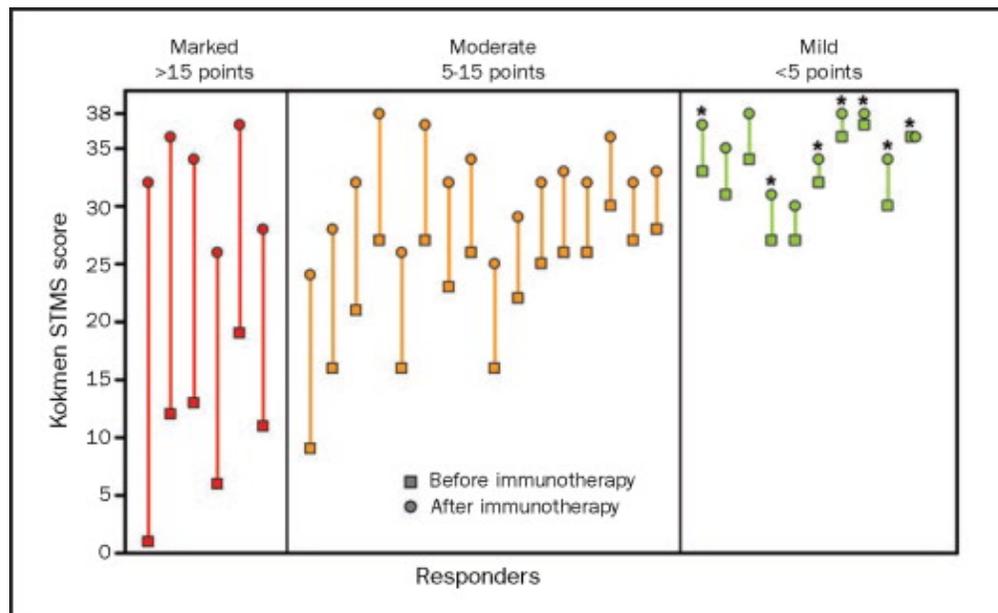
Overall we found that all 12 patients with VGKC complex antibodies responded. Two of six patients with GAD65 antibodies and 5 of 10 patients either with plasma membrane antibodies not known to be associated with encephalitis or who lacked any neural antibody were responders (Figure 2). Of 23 patients who underwent IVMP therapy as 1st line therapy, 10 were considered non-responders: IVIG therapy was administered to 5 of these non-responders and 40% had $\geq 50\%$ reduction in their seizure frequency. Of 6 receiving IVIG as 1st line therapy 33% had $\geq 50\%$ reduction in their seizure frequency. These retrospective findings justify consideration of a diagnostic trial of immunotherapy in patients with autoimmune epilepsy (with or without neural autoantibodies). Since all patients with VGKC complex antibodies receiving immunotherapy were responders, these patients will serve as the basis for this first randomized controlled trial.

In our original systematic analysis of 32 patients with suspected autoimmune epilepsy, we reported that 63% had memory and cognitive difficulties and 25% had personality change. Given this high frequency of cognitive problems, and our prior data indicating significant benefits in cognitive performance post immunotherapy in patients with autoimmune encephalopathies with or without seizures, we suggest that neuropsychological assessments be performed at baseline and after treatment. We have previously shown that autoimmune cognitive disorders also are highly responsive to immunotherapy.

In 2010, our group also treated 72 consecutive patients with suspected autoimmune cognitive disorders (all with cognitive dysfunction [amnesia, executive dysfunction, behavioral change]) as the predominant presenting symptom.¹⁵ Seizures were also encountered in 25% of the patients. Forty-six patients (64%) improved (documented in 80% by the Kokmen Short Test of Mental Status [Figure 3], neuropsychological testing [Figure 4], or both). Pretreatment and posttreatment neuropsychological score comparisons revealed improvement in almost all cognitive domains, most notably learning and memory. Immunotherapy responsiveness was predicted by a subacute onset ($p < .001$), fluctuating

course ($p < .001$), tremor ($p = .007$), shorter delay to treatment ($p = .005$), seropositivity for a cation channel complex autoantibody ($p = .01$; neuronal voltage-gated potassium channel more than calcium channel or neuronal acetylcholine receptor), and elevated cerebrospinal fluid protein (>100 mg/dL) or pleocytosis ($p = .02$). Of 26 immunotherapy-responsive patients followed up for more than 1 year, 20 (77%) relapsed after discontinuing immunotherapy. Though most received intravenous methylprednisolone as their initial therapy, 13 of 35 (37%) patients were initiated on IVIG as long-term therapy at 1-4 weekly intervals to maintain remission. In 20 patients who received long-term immunosuppression therapy, symptoms relapsed in the course of reducing the dose or increasing the interval between IV infusions of IVIG.

Figure 3. Improvements in Kokmen Short Test of Mental Status (STMS) score among responders after immunotherapy. Kokmen STMS scores improved in 32 of 46 patients responding to immunotherapy. Scores of nonresponders, by definition, did not improve. The Short Test of Mental Status (STMS)^{16,17} was developed and validated as a screening bedside mental status test specifically for use in dementia/cognitive improvement. It covers a broad range of cognitive functions and uses a 4-word learning list with a delayed recall of approximately 3 minutes.^{16,17} The construction of the recall task in the STMS was intended to make it more sensitive to the problems of learning and recall in MCI and early dementia. In addition, the STMS includes test items that better assess abstract reasoning and mental agility than the Mini-Mental State Examination (MMSE)¹⁸.



Legend indicates: *Mild postimmunotherapy improvements in Kokmen STMS score that were accompanied by significant improvements on neuropsychological testing

Figure 4. Neuropsychological evaluations before and after treatment in 6 patients positive for VGKC complex antibody. Patients 3-6 also had frequent seizures.

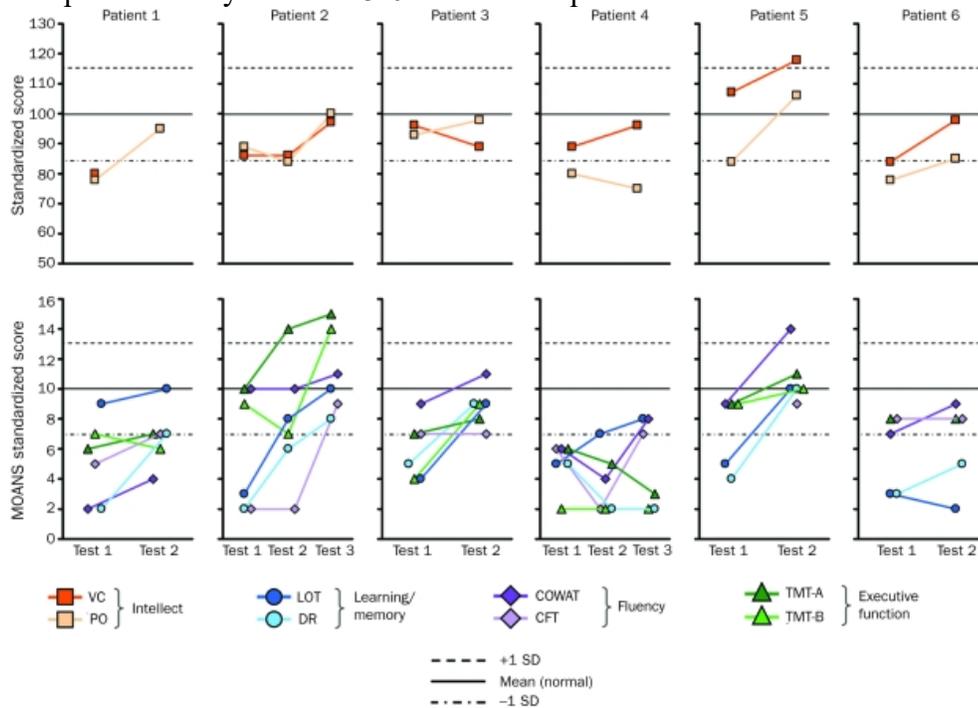


Figure 4. Neuropsychological evaluations before and after treatment in 6 patients positive for voltage-gated potassium channel (VGKC) complex antibody. Mayo Older American Normative Studies (MOANS) scale scores in 6 patients with VGKC complex antibodies illustrate the initial severity of neuropsychological impairment and post-treatment improvement.¹⁹ Patient 1 presented with severely impaired verbal memory and lexical fluency, intact verbal learning, and mild-to-moderate impairment of other indices: treatment was followed by substantial improvement in verbal memory and less impressive improvement in other scores. Patient 2 had severe impairment of verbal learning, verbal memory, and semantic fluency and showed a stepwise, protracted, but nevertheless complete recovery over 8 months. Patient 3 had impaired verbal learning and memory, semantic fluency, and executive function; all deficits except that in semantic fluency resolved after treatment. Patient 4 presented with impairment in all cognitive domains. After treatment, the patient had mild initial improvement but marked cognitive fluctuation during the next 9 months; follow-up tests showed improvement in some areas and deterioration in others. Patient 5 and 6 both had dramatic clinical improvement after treatment but relapsed within 1 month. Cognitive testing during relapse showed impaired perceptual organization (PO) and verbal learning and memory, which resolved after resumption of treatment (completely in patient 5, incompletely in patient 6). Median VGKC complex autoantibody values for these 6 patients decreased significantly from 1.04 nmol/L (range, 0.13-4.22 nmol/L; reference range, 0.00-0.02 nmol/L) to 0.14 nmol/L (range, 0.00-1.87 nmol/L) after immunotherapy. CFT=Category Fluency Test; COWAT=Controlled Oral Word Association Test; DR=delayed recall; LOT=learning over trials; TMT=Trail-Making Test; VC=verbal comprehension.

Contribution to the Field of Science:

The Autoimmune Neurology Group at Mayo Clinic has had a standardized approach to the management of patients with presumed autoimmune epilepsy. We use response to immunotherapy as a diagnostic indicator of an autoimmune etiology, and our standard practice is that patients with suspected autoimmune epilepsy undergo a treatment trial with either intravenous methylprednisolone or IVIG (preferred, given side effect profile and potential for use as maintenance therapy). Unfortunately, over the past one to two years there has been a significant increase in insurance denial for use of intravenous immunoglobulin for suspected autoimmune epilepsy. It is of paramount

importance to our patients that we show in a randomized controlled fashion that IVIG does indeed work in the diagnostic and therapeutic management of these patients. If this initial study on VGKC Ab associated epilepsy is positive and reveals a definite IVIG benefit, the information gathered will assist in the design of additional studies on autoimmune epilepsies associated with other neural antibodies. We expect that our approach would be adopted at many other centers and will have far reaching consequences for use of IVIG as a diagnostic/therapeutic tool in the evaluation of patients with suspected autoimmune CNS/PNS disorders including dementia and gastrointestinal dysmotility.

1.2 Investigational Agent

GAMUNEX®-C, [Immune Globulin IV (Human), 10% Caprylate/Chromatography Purified]

CLINICAL PHARMACOLOGY

Mechanism of Action

PI

GAMUNEX®-C supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria, viral, parasitic, mycoplasma agents, and their toxins. The mechanism of action in PI has not been fully elucidated.

ITP

The mechanism of action of high doses of immunoglobulins in the treatment of ITP has not been fully elucidated.

CIDP

The precise mechanism of action in CIDP has not been fully elucidated.

Pharmacodynamics

Immunoglobulins are fractionated blood products made from pooled human plasma. Immunoglobulins are endogenous proteins produced by B lymphocyte cells. The main component of GAMUNEX-C is IgG ($\geq 98\%$) with a sub-class distribution of IgG1, IgG2, IgG3 and IgG4 of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively.

Pharmacokinetics

Intravenous Administration

Two randomized pharmacokinetic crossover trials were carried out with GAMUNEX-C in 38 subjects with Primary Humoral Immunodeficiencies given 3 infusions 3 or 4 weeks apart of test product at a dose of 100-600 mg/kg body weight per infusion. One trial compared the pharmacokinetic characteristics of GAMUNEX-C to GAMIMUNE N, 10% and the other trial compared the pharmacokinetics of GAMUNEX-C (10% strength) with a 5% concentration of this product. The ratio of the geometric least square means for dose-normalized IgG peak levels of GAMUNEX-C and GAMIMUNE N, 10% was 0.996. The corresponding value for the dose-normalized area under the curve (AUC) of IgG levels was 0.990. The results of both PK parameters were within the pre-established limits of 0.080 and 1.25. Similar results were obtained in the comparison of GAMUNEX-C 10% to a 5% concentration of GAMUNEX-C.

The main pharmacokinetic parameters of GAMUNEX-C, measured as total IgG in study 100152 are displayed below.

Table PK Parameters of GAMUNEX®-C and GAMIMUNE® N, 10%

GAMUNEX®-C				GAMIMUNE® N, 10%				
N	Mean	SD	Median	N	Mean	SD	Median	
Cmax (mg/mL)	17	19.04	3.06	19.71	17	19.31	4.17	19.30
Cmax-norm (kg/mL)	17	0.047	0.007	0.046	17	0.047	0.008	0.047
AUC(0-tn) * (mg*hr/mL)	17	6746.48	1348.13	6949.47	17	6854.17	1425.08	7119.86
AUC(0-tn) norm * (kg*hr/mL)	17	16.51	1.83	16.95	17	16.69	2.04	16.99
T1/2† (days)	16	35.74	8.69	33.09	16	34.27	9.28	31.88

* Partial AUC: defined as pre-dose concentration to the last concentration common across both treatment periods in the same patient.

† Only 15 subjects were valid for the analysis of T1/2.

The two pharmacokinetic trials with GAMUNEX-C show the IgG concentration/time curve follows a biphasic slope with a distribution phase of about 5 days characterized by a fall in serum IgG levels to about 65-75% of the peak levels achieved immediately post-infusion. This phase is followed by the elimination phase with a half-life of approximately 35 days. IgG trough levels were measured over nine months in the therapeutic equivalence trial. Mean trough levels were 7.8 ± 1.9 mg/mL for the GAMUNEX-C treatment group and 8.2 ± 2.0 mg/mL for the GAMIMUNE N, 10% control group.

Description

GAMUNEX-C is a ready-to-use sterile solution of human immune globulin protein for intravenous and subcutaneous (PI indication only) administration. GAMUNEX-C consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. GAMUNEX-C contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. The distribution of IgG subclasses is similar to that found in normal serum. GAMUNEX-C doses of 1 g/kg correspond to a glycine dose of 0.15 g/kg. While toxic effects of glycine administration have been reported, the doses and rates of administration were 3–4 fold greater than those for GAMUNEX-C. In another study it was demonstrated that intravenous bolus doses of 0.44 g/kg glycine were not associated with serious adverse effects.⁽²²⁾ Caprylate is a saturated medium-chain (C8) fatty acid of plant origin. Medium chain fatty acids are considered to be essentially non-toxic. Human subjects receiving medium chain fatty acids parenterally have tolerated doses of 3.0 to 9.0 g/kg/day for periods of several months without adverse effects.⁽²³⁾ Residual caprylate concentrations in the final container are no more than 0.216 g/L (1.3 mmol/L). The measured buffer capacity is 35 mEq/L and the osmolality is 258 mOsmol/kg solvent, which is close to physiological osmolality (285-295 mOsmol/kg). The pH of GAMUNEX-C is 4.0–4.5. GAMUNEX-C contains no preservative and is latex-free.

GAMUNEX-C is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. Isotonicity is achieved by the addition of glycine. GAMUNEX-C is incubated in the final container (at the low pH of 4.0–4.3). The product is intended for intravenous administration and may be administered subcutaneously in treatment of PI.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model, using the following enveloped and non-enveloped viruses: human immunodeficiency virus, type I (HIV-1) as the relevant virus for HIV-1 and HIV-2; bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; pseudorabies virus (PRV) as a model for large DNA viruses (e.g., herpes viruses); Reovirus type 3 (Reo) as a model for non-enveloped viruses and for its resistance to physical and chemical inactivation; hepatitis A virus (HAV) as relevant non-enveloped virus, and porcine parvovirus (PPV) as a model for human parvovirus B19.

Overall virus reduction was calculated only from steps that were mechanistically independent from each other and truly additive. In addition, each step was verified to provide robust virus reduction across the production range for key operating parameters.

2 Study Objectives

This study evaluates the utility of IVIG in the evaluation and management of patients with suspected autoimmune epilepsy associated with voltage gated potassium channel complex autoantibodies (VGKC Ab).

Primary Aim

- To assess in a blinded randomized controlled fashion, whether 5 weeks of IVIG can reduce or stop seizures in patients with VGKC Ab associated autoimmune epilepsy.
- To evaluate the safety and tolerability of IVIG in VGKC Ab associated autoimmune epilepsy.

Secondary Aim

- To investigate clinical factors predictive of immunotherapy response.
- To assess whether IVIG improves cognitive performance [$\geq 20\%$ on Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)] in patients undergoing IVIG therapy for VGKC Ab associated epilepsy.

Tertiary Aim

To perform a 1 year observational follow up to investigate factors (including maintenance immunotherapy vs. no therapy) influencing relapse rate after positive IVIG response

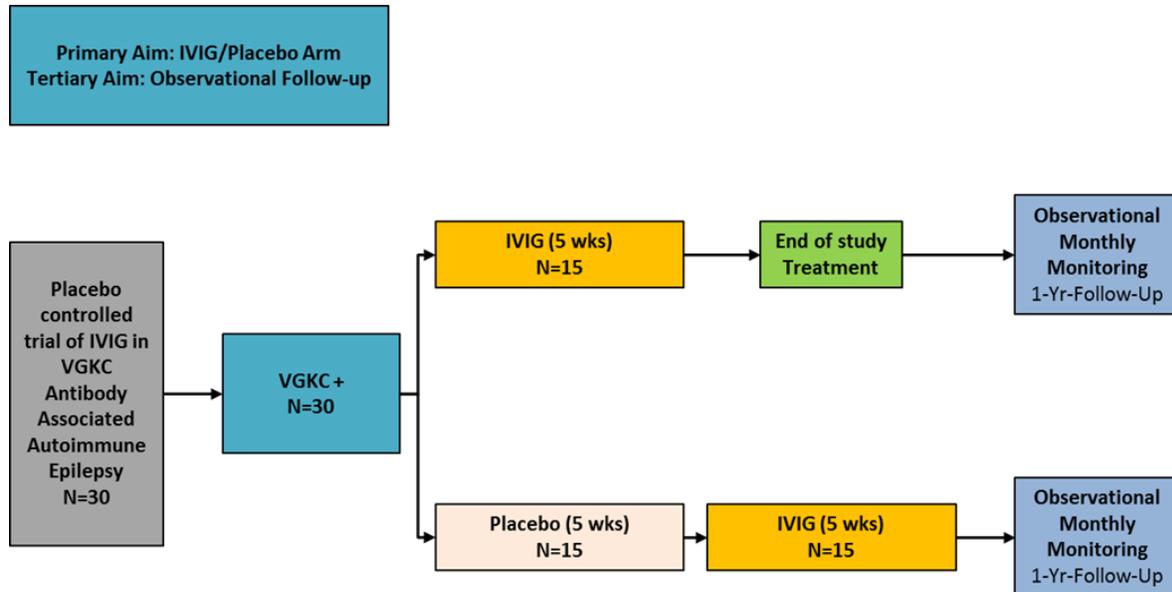
- This will be a post-trial observational follow up of all patients. The treating clinician will randomly assign patients to receive no treatment or immunotherapy.
- The immunotherapy will be mycophenolate mofetil with IVIG taper. This may be changed to alternative immunotherapies if the patient's insurance denies coverage.

3 Study Design

3.1 General Design

This study is a Phase III/IV, randomized double blind placebo controlled trial of IVIG in patients with voltage gated potassium channel complex antibody associated autoimmune epilepsy. The purpose of this study is to determine if intravenous immunoglobulin (IVIG) treatment significantly reduces the number of epileptic seizures in cases of autoimmune epilepsy. Subjects will be screened at an outpatient neurology clinic visit appointment. Interested qualified subjects will be consented and offered participation in this trial. Once consent has been obtained, and it is determined that the subject meets all inclusion criteria, the subject will be randomized to either IVIG or placebo treatment for the next 5 weeks. Subjects will return to Mayo Clinic for an evaluation. Those subjects that received the placebo for 5 weeks will be given IVIG in an open label fashion for 5 weeks (week 7-11) then return to Mayo Clinic for evaluation and collection of samples. All subjects will receive monthly phone calls after they complete the IVIG treatment for a period of 1 year from the end of IVIG 5 week course. 6 month and 12 month follow-up clinic visits would be standard of care.

3.2 Study Schematic



Patients will be randomized (1:1 ratio) to receive IVIG or placebo (normal saline). The IVIG or placebo dose will be determined based on ideal weight with a dose not to exceed 80 grams. Patients will be given 650 mg acetaminophen (Tylenol®) and Diphenhydramine (Benadryl®) 25 mg PO PRN, may repeat once after 30 minutes if ineffective, 30 minutes prior to IVIG or placebo administration at every infusion. Patients will receive IVIG or placebo (0.5g/kg) daily for 1 day [week 1 day 1], then they will receive IVIG or placebo (1g/kg not exceeding 80g) daily for 1 day [week 1 day 2]. Patients will also receive 500 ml normal saline before and after the higher dose infusion of 1g/kg. Then, once every 2 weeks [week 3 & 5], patients will receive (0.6g/kg) IVIG or placebo for 4 weeks (2 infusions). After completion of all 4 infusions all patients will be again evaluated at Mayo Clinic [week 6].

The primary aim is to demonstrate the efficacy of IVIG relative to placebo in reducing or stopping seizures [$\geq 50\%$ reduction in seizure frequency] in patients with VGKC Ab associated autoimmune epilepsy. At the end of the 5 week trial, all patients in the initial placebo group (n=15) will receive, in an open label fashion with the same premedications and prehydration protocols IVIG. To help speed up the transition for the placebo group, 1 person from the Mayo study staff, not in direct contact with patients or assessment procedures, will be unblinded, to allow for scheduling with Option Care for the future home infusions. Mayo study staff will work with Option Care to get the IVIG infusions scheduled for the placebo group as soon as possible after the patient's 6 week visit to Mayo Clinic. Option Care home infusion agency will administer these patients IVIG (0.5g/kg) 1 day [week 7 day 1] then IVIG (1g/kg not exceeding 80g) for 1 day [week 7 day 2], then once every 2 weeks for 4 weeks (0.6g/kg IVIG) [week 9 and 11]. After completion of all 4 IVIG infusions these 15 patients will be again evaluated at Mayo Clinic [week 12].

All patients will receive phone calls from the clinical research coordinator at 2 weeks, 4 weeks to assess patient reported side effects and record seizure diary information. The placebo group that will receive IVIG in an open label fashion, will also receive phone calls every week (weeks 7-11) to assess patient reported side effects and record seizure diary information. Any side effects or increase in seizure frequency from previous baseline will be reported to the principal investigator or designee to determine if any action should be taken or if un-blinding is required. Patients will also be given 24 hour emergency contact information for the study team to carry with them at all times.

Treatment location:

First 4 infusions will be given at Mayo Clinic using Mayo's standard operating procedures for infusion administration (see appendix 1). This will allow study personnel to closely evaluate the patient and give the home care network time to set the home treatment.

Home infusions:

The 4 IVIG infusions for those 15 initial placebo group patients will be given at the patient's home or clinic near their home. These infusions will be given per Option Care's standard operating procedure (see appendix 2)

In this study we are going to utilize the home care network of Option Care nationwide. Therefore one of the inclusion criteria is that the home treatment network is available where the patient lives.

Our secondary aim firstly investigates clinical factors predictive of IVIG response. These will include antibody type (LGI1, CASPR2, other) and titer. Thus blood draws will be performed at baseline, 6 weeks and 12 weeks (for placebo only). Secondly, we will assess for improvements in cognitive performance as measured by the KOKMEN¹⁷ and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).²⁰

Our tertiary aim, a clinical observational study, investigates factors influencing relapse rate after a positive IVIG response. "Responders" from AIM 1 will be randomly assigned in open label fashion by the treating physician to 2 clinical observational groups:

- Immunotherapy (as per physician/insurance approval): mycophenolate mofetil 2000mg daily or azathioprine 2mg/kg +/- IVIG taper or IVMP taper
- No immunotherapy

Patients will keep a daily seizure diary. Patients will be seen at 6 months and 12 months as part of standard clinical care (neurological examination will be recorded). A study coordinator will call patients every month after completion of the study infusions to review seizure history, medications, and adverse events. Relapse will be defined as $\geq 20\%$ increase in seizure frequency (# seizures per week) compared with the post IVIG weekly seizure frequency. Cognition will be assessed by the study coordinator who will perform Telephone Interview for Cognitive Status (TICS) and the KOKMEN at each monthly call.²¹

If a relapse occurs, the patient will be seen at the clinic as standard of care. Patients on no therapy will be started on immunotherapy per current standard of care. Those on therapy will have treatment adjusted as per current standard of clinical care.

3.3 Primary Study Endpoints

Reduction of 50% or more, in seizure frequency with IVIG treatment.

3.4 Secondary Study Endpoints

Improvement of 20% or more in cognitive function measured by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

3.5 Primary Safety Endpoints

- IVIG is a well-known drug and is used routinely in medical practice. We will however as a part of the primary endpoints evaluate the safety and tolerability of IVIG in VGKC Ab associated autoimmune epilepsy.

4 Subject Selection Enrollment and Withdrawal

Target accrual: 30 participants

4.1 Inclusion Criteria

- Seropositivity for VGKC complex antibodies (value $>0.1\text{nM}$; normal $\leq 0.02\text{nM}$) or positive for LGI1/CASPR2 Ab by CBA.
- And ≥ 2 seizures per week (mean of total over 1 week)
- Male or female between the ages of 18 and 85 years of age
- Women and men of child bearing potential must agree to use a reliable form of contraception throughout the course of the study.
- Homecare treatment agency available at place of residence, or agreeable to travel to Mayo Clinic in the rare event of unavailability of the homecare agency. (This information will be known by the patient and study team before consenting to the study).
- On a stable dose of antiepileptic medications (unable to change while receiving IVIG/placebo) or on no treatment

4.2 Exclusion Criteria

- History of thrombotic episodes within the 2 years prior to enrolment
- History of status epilepticus within the last year
- Known allergic or other severe reactions to blood products including intolerance to previous IVIG
- Previous adequate trial of IVIG as determined by the Principal Investigator
- IgA deficiency
- Prior failed trial of high dose steroid (prednisone $>60\text{mg}$ daily or methylprednisolone $>1\text{g}$ weekly for >2 weeks)
- Reproductive status:
 - Women who are pregnant,
 - Women who are breastfeeding,
 - Women and men of childbearing potential who are unwilling or unable to use an acceptable method of birth control to avoid pregnancy for the entire study period, as evaluated by the investigator. (Women of non-childbearing potential are those that have a history of hysterectomy, bilateral oophorectomy, or are postmenopausal with no history of menstrual flow for > 12 months prior to screen visit.)
- Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
- Evidence of serious uncontrolled concomitant diseases that may preclude patient participation (physician determined), as described; Other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency
- Known active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline.
- Evidence of chronic active hepatitis B or C.
- Active ischemic heart disease in the past year prior to baseline.
- Patients should not have severe renal or hepatic disease (determined by treating physician).
- Severe hypertension (diastolic pressure >120 mmHg or systolic >170 mmHg).

4.3 Subject Recruitment, Enrollment and Screening

Since our preliminary data indicate a high likelihood of response (80-100%) for patients with VGKC Abs we intend to randomize 30 patients to allow a powered study. Patients will be identified through Mayo Clinic's Neuroimmunology Laboratory [100,000 patients sera tested annually for neural

autoantibodies (~10,000 positive) on a clinical service basis], Autoimmune Neurology Clinic's close interactions with the Epilepsy neurology groups, and referrals through ClinicalTrials.gov website. Patients will be asked to keep a daily seizure diary (minimum of 1 week), before they come for their first evaluation at Mayo Clinic.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients are allowed to withdraw consent at any time. Every effort should be made to ensure patients are willing to comply with trial participation prior to conducting the screening procedures and the patients should be fully informed of the restrictions related to the change of concomitant medications during the trial. Investigators may choose to discontinue a patient's treatment because of AEs, as well as conditions or illnesses that preclude compliance with the protocol from the standpoint of the patient's safety or well-being. The study staff should notify the Sponsor of all trial withdrawals as soon as possible. The reason for patient discontinuation must be recorded in the source documents and CRF.

Reasons subjects may be withdrawn from this research study

- Subject safety issues
- Failure of subject to adhere to protocol requirements
- Disease progression or a 50% increase in seizure frequency (compared to baseline).
- Subject decision to withdraw from the study (withdrawal of consent)
- Severe allergic reaction that call for hospitalization.
- Any thrombotic event
- Status epilepticus

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

When a patient withdraws or is withdrawn from the trial, the Investigator shall record the withdrawal reason(s) in the source documents and CRF. Whenever possible, all patients who prematurely withdraw from the trial will undergo all assessments at the early termination visit.

If a patient is discontinued due to an AE, the event will be followed until it is resolved or in the opinion of the PI the patient is determined to be medically stable. Every effort will be made to undertake protocol-specified safety follow-up procedures. Patients who fail to return for final assessments will be contacted by the site study staff to be reminded of the necessary follow-up. As it is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE, follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the patient's last known address. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

5 Study Drug

5.1 Description

GAMUNEX-C is clear a ready-to-use sterile solution of human immune globulin protein for intravenous administration.

5.2 Treatment Regimen

Patients will maintain their stable dose of antiepileptic medications while receiving IVIG or placebo. Patients will be randomized (1:1 ratio) to receive IVIG or placebo (normal saline). The IVIG or placebo dose will be determined based on ideal weight with a dose not to exceed 80 grams. Patients will be given 650 mg acetaminophen (Tylenol®) and Diphenhydramine (Benadryl®) 25 mg PO PRN, may repeat once after 30 minutes if ineffective, 30 minutes prior to IVIG or placebo administration at

every infusion. Patients will receive IVIG or placebo (0.5g/kg) daily for 1 day [week 1 day 1], then they will receive IVIG or placebo (1g/kg not exceeding 80 gr) daily for 1 day [week 1 day 2]. Patients will also receive 500 ml normal saline before and after the higher dose infusion of 1g/kg. Then once every 2 weeks patients will receive 0.6g/kg IVIG or placebo for 4 weeks [week 3 and 5] for 2 infusions. After completion of all 4 infusions all patients will be again evaluated at Mayo Clinic [week 6].

The primary aim is to demonstrate the efficacy of IVIG relative to placebo in reducing or stopping seizures [$\geq 50\%$ reduction in seizure frequency] in patients with VGKC Ab associated autoimmune epilepsy. At the end of the 5 week trial, all patients in the initial placebo group (n=15) will receive, in open label fashion with the same premedications and prehydration protocols IVIG. To help speed up the transition for the placebo group, 1 person from the Mayo study staff, not in direct contact with patients or assessment procedures, will be unblinded, to allow for scheduling with Option Care for the future home infusions. Mayo study staff will work with Option Care to get the infusions scheduled for the placebo to IVIG group as soon as possible after the patient's 6 week visit to Mayo Clinic. Option Care home infusion agency will administer these patients IVIG (0.5g/kg not exceeding 80 gr) 1 day [week 7 day 1] then IVIG (1g/kg not exceeding 80 gr) for 1 day [week 7 day 2], then once every 2 weeks for 4 weeks (0.6g/kg IVIG) [week 9 and 11]. After completion of all 4 IVIG infusions these 15 patients will be again evaluated at Mayo Clinic [week 12].

5.3 Method for Assigning Subjects to Treatment Groups

All patients who are cleared for randomization by their Principal Investigator (PI) or the Sub-Investigator will be randomized on Day 1. The research pharmacy will be performing the 1:1 (drug/placebo) randomization. All patients must remain on randomized treatment assignment until their EOS or Early Termination (ET) Visit.

5.4 Preparation and Administration of Study Drug

- Preparation of the study drug will be done at the research pharmacy
- The drug or placebo will be placed in bags and sent to the infusion center for administration.
- Contact names and Phone number for the Research Pharmacy:

[REDACTED]

5.5 Prior and Concomitant Therapy

- Medication history will be collected for the 2 years prior to entering the trial
- Concomitant medical therapy will be collected throughout the entire year of the trial
- Study subjects are not allowed to start any new immunosuppressant therapy or change their antiepileptic medications during their participation in the primary aim of the trial when they are receiving the IVIG or placebo

5.6 Packaging

- The drug will be shipped by Grifols to the research pharmacy at Mayo Clinic
- The saline placebo will be clear in appearance to match the appearance of Gamunex-C®
- The drug will be shipped in glass vials (20 g, 10 g and 5 g)
- The drug will be mixed in plastic bags for administration at the Mayo infusion center.
- The bags will be labeled by Mayo's Research Pharmacy in accordance with all laws and state "Gamunex-C® or Placebo"

5.7 Masking/Blinding of Study

The entire Mayo study team, investigator, and the nurse administering the drug at Mayo's infusion center will be blinded (double-blind). Only the research pharmacy and one unblinded Mayo study team member without patient contact will know which subjects will be receiving actual drug, and which subjects will be receiving placebo.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Grifols will ship the Gamunex-C® to Mayo Clinic's Research Pharmacy in Rochester, MN. Upon receipt of the of the study treatment drug, an inventory must be performed and a drug receipt log filled out by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment will be documented in the study files. The sponsor (Grifols) and the investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

5.8.2 Storage

The study drug will be stored at the research pharmacy. Temperature logs will be kept and monitored as required.

5.8.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the pharmacy and study team.

5.8.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Visit 1 (Screening)

The following will occur at this visit and last up to 4 hours

- Review of medical history
- Review of past and current medication history
- Vital signs (blood pressure, temperature, heart rate, breathing rates, height and weight)
- Neurologic examination
- Undergo memory and cognitive function assessments (RBANS/ KOKMEN Neuropsych testing)
- Review seizure diary
- Confirmation of stable dose of antiepileptic medications

After the assessments are complete and if the subject still meets all study inclusion criteria blood will be drawn for testing. The amount of blood drawn will be approximately 6 tablespoons or 90mL.

This blood test will look at the following:

- kidney and liver function
- Blood sugar and electrolytes

- IgA immunoglobulins
- Antibody testing
- A pregnancy test if you are a female and able to become pregnant
- Blood for repository for future testing

6.2 Visit 2 & 3; Week-1 Day 1 and Day 2

Mayo Clinic Infusions

Within a few days after the subjects initial evaluation they will receive the first two infusions at the Mayo Clinic Infusion Center. The first infusion (0.5g/kg) drug or placebo will be followed by the second infusion (1g/kg) being given the very next day.

The IVIG infusion is given over approximately 6-8 hours depending on the dose and rate of the infusion. Prior to the infusion the subject will have an intravenous catheter (IV) placed in the subjects arm which will be removed after each infusion is completed.

The subject will be given IV fluids (500 mls of normal saline) before and after the infusion of 1g/kg. The subject will be given acetaminophen (Tylenol) (to prevent headache) and Benadryl (to prevent allergic reaction) before all infusions. Before, during and after the infusions, the subject's vital signs will be monitored.

6.3 Visit 4 & 6; Weeks 2 & 4

Phone Calls

The subject will receive a phone call from the study coordinator at week-2 and again at week-4. During these phone calls, the study coordinator will review the subjects seizure history, medications changes (started any new or stopped any medication), or had any adverse events (side effects, illness, and/or hospitalizations).

6.4 Visit 5 & Visit 7; Week-3 and Week-5

Mayo Clinic Infusion Center

Week-3 infusion (0.6g/kg drug or placebo) will be given 2 weeks following the 2nd infusion. Week-5 (0.6g/kg drug or placebo) infusion will be given 2 weeks after the 3rd infusion (total of 5 weeks).

6.5 Visit 8; Week 6

Mayo Clinic Examination and Unblinding.

During this visit, patients will be seen in clinic. All required assessments will be documented and signed.

- Review current medication history
- Vital signs (blood pressure, temperature, heart rate, breathing rates, and weight)
- Neurological Examination
- Undergo memory and cognitive function assessments (RBANS/KOKMEN- Neuropsych testing)
- Blood draw to check antibody levels.
- Review Seizure Diary

Then, the study physician and the subject will be unblinded.

If the study subject received placebo, they will be given IVIG in an open label fashion through Option Care Home Infusion service using the same dose and schedule as used for the first portion of this study. The last 4 IVIG infusions for those 15 patients, who received placebo for the first 4 treatments, will be given at the patient's home or clinic near their home. These infusions will be given per Option Care's standard operating procedure. In this study we are going to utilize the home care network of Option Care nationwide. Therefore one of the inclusion criteria is that the home treatment network is available where the patient lives.

If the study subject received IVIG, this will be their Research clinic visit, and they will NOT receive any more infusions for the study, they will only receive the phone calls for long term follow up and proceed to VISIT 16, 26 of the tertiary aim.

6.6 Visit 9 & 10; Week 7: Day 1/Day 2

Option Care Home Infusion

Within a 7-10 days after the subjects Week6 evaluation they will receive the first two infusions through Option Care. The first infusion (0.5mg/kg) IVIG will be followed by the second infusion (1g/kg) being given the very next day.

The IVIG infusion is given over approximately 6-8 hours depending on the dose and rate of the infusion. Prior to the infusion the subject will have an intravenous catheter (IV) placed in the subjects arm which will be removed after each infusion is completed.

The subject will be given IV fluids (500 mls of normal saline) before and after the infusion of 1g/kg. The subject will be given acetaminophen (Tylenol) (to prevent headache) and Benadryl (to prevent allergic reaction) before all infusions. Before, during and after the infusions, the subject's vital signs will be monitored and documented by Option Care. This information will be send to Mayo Clinic for the study records.

6.7 Visit 9-14; Weeks 7-11

Phone Calls

The subject will receive a phone call from the study coordinator every week (week 7-11). During these phone calls, the study coordinator will review the subjects seizure history, medications changes (started any new or stopped any medication), or had any adverse events (side effects, illness, and/or hospitalizations).

6.8 Visit 12 & 14; Week-9 and Week-11

Option Care Home Infusions

Week-9 infusion (0.6g/kg IVIG) will be given 2 weeks following the 2nd infusion. Week-11 (0.6g/kg IVIG) infusion will be given 2 weeks after the 3rd infusion (total of 5 weeks).

6.9 Visit 15; Week 12

Mayo Clinic Examination

During this visit, patients will be seen in clinic. All required assessments will be documented and signed.

- Review current medication history
- Vital signs (blood pressure, temperature, heart rate, breathing rates, and weight)
- Neurological Examination
- Undergo memory and cognitive function assessments (RBANS/KOKMEN- Neuropsych testing)
- Blood draw to check antibody levels.

- Review Seizure Diary

6.10 Visits 16-31; Weeks 16-56 (IVIG group), Visits 16-60 (Placebo group)

Subjects will be contacted by phone by the study coordinator every four weeks starting at week 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56 and week 60 (only Placebo group). During each of these phone calls, the study coordinator will review the subjects seizure history, medications changes (started new or stopped any medications), or had any adverse events (side effects, illness, and/or hospitalizations). The study coordinator will also use the Telephone Interview for Cognitive Status (TICS) questionnaire and the KOKMEN. This is a questionnaire that will ask you to perform certain tasks like subtracting numbers, recalling information and following directions.

6.11 Visits 21 Week 32 (IVIG group), Visit 23 Week 38 (Placebo group)

Mayo Clinic Examination (standard of care) – following 6 months of follow-up.

During this visit, patients will be seen in clinic. All required assessments will be documented and signed.

- Review current medication history
- Vital signs (blood pressure, temperature, heart rate, breathing rates, and weight)
- Neurological Examination
- Blood draw to check antibody levels.
- Review Seizure Diary

6.12 Visits 29 Week 58 (IVIG group), Visit 31 Week 64 (Placebo group)

Mayo Clinic Examination (standard of care) – following the completion of 1 year of follow-up.

During this visit, patients will be seen in clinic. All required assessments will be documented and signed.

- Review current medication history
- Vital signs (blood pressure, temperature, heart rate, breathing rates, and weight)
- Neurological Examination
- Blood draw to check antibody levels.
- Review Seizure Diary

6.13 Early Termination Visit

Mayo Clinic Examination

During this visit, patients will be seen in clinic. All required assessments will be documented and signed. If the patient is unwilling or unable to come to Mayo Clinic, we will attempt to complete as much of the visit over the phone as possible.

- Review current medication history
- Vital signs (blood pressure, temperature, heart rate, breathing rates, and weight)
- Neurological Examination
- Undergo memory and cognitive function assessments (RBANS/KOKMEN- Neuropsych testing)
- Blood draw to check antibody levels.
- Review Seizure Diary

6.14 Primary Aim Study Procedures Schedule

Primary Aim	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Procedures	Baseline Visit Randomize 1:1 to IVIG or Placebo (all)	Week-1 Day 1 Mayo Infusion Center	Week-1 Day 2 Mayo Infusion Center	Week 2	Week 3 Mayo Infusion Center	Week 4	Week 5 Mayo Infusion Center
Inclusion/Exclusion Criteria Review	B						
Informed Consent	B						
Medial History	B						
Medication Review	B	B	B	B	B	B	B
Seizure History	B						
Safety Labs (Renal, Hepatic, Chem, IgA)	B						
Antibody Testing (VGKC, LGI1, CASPR2)	B						
Neuropsych Testing (RBANS/KOKMEN/TICS)	B						
Vital Signs (B/P, Temp, Height/Weight)	B	B	B		B		B
Infusion Therapy		B	B		B		B
Study Visit (Clinic)	B						
Seizure Diary/Adverse Events	B	B	B	B	B	B	B
Phone Call				B		B	

B=Both IVIG and Placebo groups

I=IVIG group only

P=Placebo at baseline group

SOC=standard of care

P* only in case of abnormal results at baseline as determined by treating physician.

All visits for the Primary Aim have a +/- 3 day window.

All visits for the Tertiary Aim have a +/- 7 day window.

Primary Aim	Crossover Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
Procedures	Week 6 EOS for IVIG Group Start SOC	Week-7 Day 1 Option care home infusion	Week-7 Day 2 Option care home infusion	Week 8	Week 9 Option care home infusion	Week 10	Week 11 Option care home infusion	Week 12 end of Study Visit Placebo Group-Start SOC
Inclusion/Exclusion Criteria Review								
Informed Consent								
Medial History								
Medication Review	B	P	P	P	P	P	P	P
Seizure History	B							P
Safety Labs (Renal, Hepatic, Chem, IgA)	p*							
Antibody Testing (VGKC, LGI1, CASPR2)	I							P
Neuro psych Testing (RBANS/KOKMEN/TICS)	B							P
Vital Signs (B/P, Temp, Height/Weight)	B	P	P		P		P	P
Infusion Therapy		P	P		P		P	
Study Visit (Clinic)	B							P
Seizure Diary/Adverse Events	B	P	P	P	P	P	P	P
Phone Call		P	P	P	P	P	P	

6.15 Tertiary Aim Study Procedures Schedule

Tertiary Aim	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23
Procedures	Week 10	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 38
Phone Call Follow up	I	B	B	B	B	B	B	
Seizure Diary/Adverse Events	I	B	B	B	B	B	B	
Medication Review	I	B	B	B	B	B	B	
TICS/KOKMEN	I	B	B	B	B	B	B	
Antibody Testing (VGKC, LGI1, CASPR2)						I		P
Standard of Care visit at Mayo Clinic						I		P

TICS=Telephone interview for cognitive status

Tertiary Aim	Visit 24	Visit 25	Visit 26	Visit 27	Visit 28	Visit 29	Visit 30	Visit 31
Procedures	Week 40	Week 44	Week 48	Week 52	Week 56	Week 58	Week 60	Week 64
Phone Call Follow up	B	B	B	B	B		P	
Seizure Diary/Adverse Events	B	B	B	B	B		P	
Medication Review	B	B	B	B	B		P	
TICS/KOKMEN	B	B	B	B	B		P	
Antibody Testing (VGKC, LGI1, CASPR2)						I		P
Standard of Care visit at Mayo Clinic						I		P

7 Statistical Plan

7.1 Statistical Methods

Dr. [REDACTED], senior statistician and Professor of Biostatistics, will be responsible for analyzing study data. The treatment (IVIg or placebo) will be unblinded at the 6 week follow up.

Randomized Placebo Controlled Trial:

The study will include 30 patients (15 per arm). Data collected will be summarized using descriptive statistics such as mean, standard deviation, median, minimum and maximum for continuous variables and using frequencies and percentages for categorical variables (see Study Endpoints). Primary outcome, which is binary variable, i.e. proportion of patients responding to treatment (yes, no) will be estimated along with 95% exact binomial confidence intervals for each arm of the respective study. These proportions will then be compared using Fisher's exact test within the study. Continuous outcomes of interest will be compared using two sample t-test or Wilcoxon rank sum test as appropriate.

Multiplicity

Due to smaller sample sizes, no adjustment for multiple comparisons is done.

Power/Sample Size

Sample size and power calculations for various scenarios using Nquery advisor software version 7.0 are provided below.

VGKC complex antibody positive

Based on preliminary data, assuming 70% responders on IVIG vs. 10% on Placebo, a total sample size of 30 (i.e.15 per group) will have 89% power at an alpha level of 5% using Fisher's exact test.

Dropouts

If we assume a maximum dropout rate of 20%, we would still maintain >80% power. In an event if the dropout rate exceeds anticipated rate, we would still have 82% power to detect hypothesized difference (70% versus 10%) with as few as 12 patients per group.

Effect of patient enrolment on power analysis in Randomized Placebo Controlled Trial

Group 1: Assuming the rate of positive response to IVIG and placebo is 70% and 10%, respectively:

Two group Fisher's-exact test of equal proportions (odds ratio = 1) (equal n's)

	1	2	3	4
Power (%)	82	89	94	97
n per group	12	15	17	19

7.2 Endpoints

Primary endpoints*

- 1) Change in seizure frequency

The definition of a “responder” is a patient with a $\geq 50\%$ reduction in seizure frequency.

Secondary endpoints

Clinical factors predictive of immunotherapy response.

The following clinical factors will be analyzed with respect to prediction/correlation with favorable outcome.

- 1) Interval from symptom onset to immunotherapy treatment
- 2) Type of onset
- 2) Clinical course
- 3) Seizure type and frequency
- 4) EEG abnormalities
- 5) Presence of other neurological symptoms or signs (tremor, headache, myoclonus)
- 6) CSF findings (White cell count; protein)
- 7) Neural autoantibody type (LGI1, CASPR2, other) and titer (blood draws will be performed at baseline, 6 weeks and 12 weeks (for placebo group only)
- 8) Change in The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scale scores

Tertiary endpoints

For the 1 year follow up “observational study”

- “Responder” patients from Trial will be randomly assigned to 2 clinical groups:
 - Immunotherapy (as per physician/insurance approval): mycophenolate mofetil 2000mg daily or azathioprine 2mg/kg +/- IVIG taper or IVMP taper
 - No immunotherapy
- Subjects will be followed for relapse for a total of 12 months (see study schedule of events).
- Patients will keep a daily seizure diary and record any adverse events while on immunotherapy.
- The study coordinator will call patients every month review seizure history and adverse events.
- Patients will be seen at 6 months and 12 months as part of standard clinical care-neurological examination will be recorded.
- Relapse will be defined as $\geq 20\%$ increase in seizure frequency compared with post IVIG frequency.
- Cognition will be assessed by the study coordinator who will perform Telephone Interview for Cognitive Status and the KOKMEN at each monthly call.
- If relapse occurs, the patient will be seen at the clinic. Patients on no therapy will be started on immunotherapy, those on therapy will have treatment adjusted as per current standard clinical care.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as (7) days following the last administration of study treatment. The study period during which adverse events must be reported is defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) and Adverse Event Report Form. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Reminder: According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

The following information will be collected for documentation of adverse events.

Information collected on the adverse event worksheet (*and entered in the research database*):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.4 Unmasking/Unblinding Procedures

While the safety of the subject always comes first, it is still important to seriously consider if unmasking/unblinding the study therapy is necessary to ensure a subject's safety.

- The need for unmasking/unblinding of study therapy on a subject will be determined by the PI
- Documentation of Unmasking/unblinding will be in the subject's source document.
- In most cases, the unmasking/unblinding will be part of managing an SAE, and will be reported with the SAE.
- However, in cases where unmasking/unblinding was not associated with an SAE, such actions should be reported in a timely manner (7 days). While there is no regulation governing this timeline, it is suggested to use the same timeline requirements for reporting of SAEs.

8.5 Stopping Rules

Autoimmune epilepsy in the presence of anti VGKC antibodies has not been proved to respond better to IVIG than to no treatment at all. There has not been an open label or a phase 3 trial regarding treatment and outcome, and there are no guidelines or recommendations regarding treatment. There is only level III evidence to support treatment in these patients. Moreover, some patients spontaneously recover back to baseline. Since not easy to diagnose (because of the presenting symptoms often being non convulsive), many times treatment is started months after symptoms start and still prognosis is

good. Therefore we feel comfortable to delay treatment for 5 weeks in the placebo group. We did however decide on stopping rules to prevent any serious implications of delaying treatment.

All participants shall have contact information for the study coordinator. Any adverse event should be reported to the coordinator within 24-48 hours by the patient. The principle investigator will be informed and take the proper steps to ensure patient safety.

1. Severe allergic reaction that call for hospitalization.
2. Any thrombotic event
3. Status epilepticus
4. Increased seizure frequency (more than 50% compared to base line).

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 “Study Monitoring, Auditing, and Inspecting”). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Plan

1. Subject Safety

All subjects enrolled into this study will undergo safety assessments (vital signs, weight, safety blood tests, and cardiac status) at various time points throughout the study. Any abnormal finding will be reported to the PI immediately upon receiving the results.

Subjects will receive phone calls the week after their infusions in which study seizure diaries will be reviewed at all visits for adverse events and any addition or stoppage of new or current medications. This information will be documented in the subject’s study binder. Any information that is collected and is considered abnormal will also be reported to the PI as soon as possible.

All participants shall have contact information for the study coordinator. Any serious adverse event should be reported to the coordinator within 24-48 hours by the patient. The principle investigator will be informed and take the proper steps to ensure patient safety (reporting to the IRB per institutional guidelines and reporting to the sponsor).

1. Severe allergic reaction that call for hospitalization.
2. Any thrombotic event
3. Status epilepticus
4. Increased seizure frequency (more than 50% compared to base line)

In the event PI is not available, the Co-Investigator will be notified of any abnormal findings.

2. Data Integrity

Study inclusion and exclusion will be reviewed with each potential subject to ensure appropriateness for enrollment into the study. Study documents will be completed at the time of the visit and will be entered into the EDC (electronic data capture) system. All data queries will be adjudicated in a timely manner to ensure transcription of data is accurate and complete. The study monitor will have access to the study files and visits to the laboratory and pharmacy will be pre-arranged for the monitor. The PI/Co-I and study team will be available during the monitoring visits.

3. Subject Privacy

Subjects will be seen on Mayo-8 in a clinical exam room. All subjects will have the study explained to them in detail by a qualified member of the study team. The signing of the consent will not occur until all subjects and/or other family members have had ample time to review the consent form and have all their questions answered by the study team.

4. Data Confidentiality

Study binders will be kept in a secure area that is limited to authorized study personnel and admittance to this area is by cardkey access only. Study data will be entered into the EDC (electronic data capture) system. Study data will be identified by a study id and subject initials. A master screening/enrollment log of all subjects screened/enrolled with identifiers will be kept electronically and separate from the study regulatory binder until the study is completed. This will be kept on a secure Mayo server and can only be accessed by Mayo study personnel.

5. Product Accountability

The study drug that is being supplied by the sponsor will be stored and dispensed by the Mayo Research Pharmacy to the study staff. The Mayo Research Pharmacy will maintain all the necessary drug accountability logs such as receipt of drug, dispensation of drug, and temp logs. The monitor will have access to view at any monitoring visit. It is the study staff's responsibility to instruct the subject on the study medication, dose of medication, route of administration, possible side effects, and who to contact in the event of side effects or questions. This will be documented in the study binder as well as the subject's EMR.

6. Study Documentation

All requires study reports will be submitted in a timely manner either to the sponsor and/or the IRB. The regulatory binder will be kept up to date and will be stored in a secure area (same area as study binders). Only authorized study staff, monitors, or other required personnel will have access to the regulatory binder.

7. Study Coordination

A roles and responsibility log will be maintained for the study. A training log that documents the staff training will also be maintained. The staff will receive protocol specific training during the Investigator's meeting as well as complete any sponsor required on-line training. Study staff will ensure that all Mayo required training is completed as it pertains to the study (protection of human subjects). Only those study team members who have completed the appropriate training will perform study specific tests and procedures.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, 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 trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –“Retention of and Access to Research Data Policy” [REDACTED]

Whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

As a service to the sponsor-investigator, this study may be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

Grifols shared services north America, INC will pay the Principal Investigator or the institution to cover costs related to running the study. Grifols will also be providing the Gamunex-C (IVIG) for the study. Option Care will be providing the home infusions for the study's open label administration of IVIG without charge for services or supplies to Mayo Clinic or the patient.

12.2 Subject Stipends or Payments

Subjects will receive up to \$2000 reimbursement for travel, lodging, and parking if they complete all of the study visits in first 12 weeks of the study and provide original receipts. If they start the study but stop before finishing the study for any reason, they will receive part of this money.

13 References

1. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011 Sep 8;365(10):919-26.
2. Granerod J, Cousens S, Davies NW, Crowcroft NS, Thomas SL. New estimates of incidence of encephalitis in England. *Emerg Infect Dis*. 2013;19(9).
3. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010 Dec;10(12):835-44.
4. Bien CG, Urbach H, Schramm J, et al. Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. *Neurology*. 2007 Sep 18;69(12):1236-44.
5. Hoffmann LA, Jarius S, Pellkofer HL, et al. Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. *J Neurol Neurosurg Psychiatry*. 2008 Jul;79(7):767-73.
6. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain*. 2004 Mar;127(Pt 3):701-12.
7. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain*. 2001 Jun;124(Pt 6):1138-48.
8. Quek AM, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. *Arch Neurol*. 2012 May;69(5):582-93.
9. Toledano M, Britton JW, McKeon A, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. *Neurology*. 2014 May 6;82(18):1578-86.
10. Ong MS, Kohane IS, Cai T, Gorman MP, Mandl KD. Population-level evidence for an autoimmune etiology of epilepsy. *JAMA Neurol*. 2014 May;71(5):569-74.
11. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain*. 2010 Sep;133(9):2734-48.
12. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol*. 2010 Aug;9(8):776-85.
13. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol*. 2014 Mar;13(3):276-86.
14. Ruegg S, Panzer JA. Immune therapy for pharmaco-resistant epilepsy: ready to go? *Neurology*. 2014 May 6;82(18):1572-3.
15. Flanagan EP, McKeon A, Lennon VA, et al. Autoimmune dementia: clinical course and predictors of immunotherapy response. *Mayo Clin Proc*. 2010 Oct;85(10):881-97.

16. Kokmen E, Naessens JM, Offord KP. A short test of mental status: description and preliminary results. *Mayo Clinic Proc* 1987; 62(4):281-288.
17. Kokmen E, Smith GE, Petersen RC, Tangalos E, Ivnik RC. The short test of mental status. Correlations with standardized psychometric testing. *Arch Neurol* 1991;48(7):725-728.
18. Tang-Wai DF, Knopman DS, Geda YE, Edland SD, Smith GE, Ivnik RJ, Tangalos EG, Petersen RC. Comparison of the short test of mental status and the mini-mental state examination in mild cognitive impairment. *Arch Neurol* 2003;60:1777-1781.
19. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological testing norms above age 55: COWAT, BNT, MAE TOKEN, WRAT-R Reading, AMNART, Stroop, TMT, and JLO. 10 ed; 1996:262-278.
20. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998 Jun;20(3):310-9.
21. Brandt J, Spencer M, Folstein M. The Telephone Interview for Cognitive Status. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology*. 1988;1(2):111-7.
22. Tai VM, Mitchell EJ, Lee-Brotherton V, Manley JJ, Nestmann ER, Daniels JM. Safety 844 evaluation of intravenous glycine in formulation development. *J Pharm Pharmaceut Sci*. 2000;3:198.
23. Traul KA, et al. Review of the toxicologic properties of medium-chain triglycerides. *Food Chem Toxicol*, 2000. 38(1): p. 79-98.