STUDY PROTOCOL

Official title: iSTAND: IVIG (Gamunex-C) Study of Treatment for Autoimmune Neuropathic Dysautonomia/Postural Tachycardia (POTS)

NCT number: NCT03919773

IRB Approved date: 12-11-19

Form A

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PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

The purpose of this trial is to evaluate the symptomatic benefits of immunomodulatory treatment with IVIG for POTS (postural tachycardia syndrome) patients with evidence of autoimmunity.

Specific aims:

Our primary aim is to determine if treatment with IVIG (Gammunex-C) is superior to active placebo (intravenous albumin) in improving the symptoms of POTS.

We propose a double-blind placebo controlled crossover pilot study of IVIG for the treatment of POTS. We will enroll subjects who meet the consensus criteria for POTS diagnosis (Sheldon et al. 2015) who have moderate to severe symptom burden and also have clinical or laboratory evidence of autoimmunity.
Secondary aims are to determine if IVIG treatment improves objective clinical measures and to evaluate the utility of clinical and laboratory measures to identify patients most likely to respond to therapy

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Postural tachycardia syndrome (POTS) is the most common autonomic disorder (Low et al. 2009) with prevalence estimated at 170/100,000 in the United States (Schondorf et al. 1999). POTS appears to be a heterogeneous syndrome that can arise from multiple distinct mechanisms and has been divided into several subtypes based on these proposed mechanisms (Benarroch 2012). One subtype is referred to as neuropathic subtype which describes the group of POTS with evidence of peripheral denervation in their lower extremities (Benarroch 2012). Evidence of peripheral nerve dysfunction can be detected on neurologic exam, through sudomotor testing and/or skin biopsy to evaluate intraepidermal small nerve fiber density. Within the neurogenic subgroup, a smaller subset may have an underlying autoimmune mechanism contributing to the development of both the neuropathy and POTS. These patients may report a preceding viral illness or other physiological stressor (such as immunization, pregnancy, injury, or minor surgery), may have elevated levels of one or more serum autoantibodies, co-existing

autoimmune disorders (including Sjogren's syndrome), or other clinical features suggesting autoimmunity (Thieben et al. 2007). A review of 100 POTS patients showed that there was higher prevalence of autoimmune markers and co-morbid autoimmune disorders in POTS patients compared to the general population with 25% having positive ANA, 7% with antiphospholipid antibody and 20% with co-morbid autoimmune disorders (Blitshteyn 2015).

Gammunex-C, a form of intravenous immunoglobulin (IVIG), is approved for the treatment of chronic inflammatory demyelinating neuropathy (CIDP) or idiopathic thrombocytopenic purpura (ITP) (see attached package insert). IVIG has been in use for many decades in the treatment of these disorders and many other inflammatory/autoimmune diseases. It is generally very safe and well tolerated. More recently, IVIG has been proposed as an effective treatment for presumed inflammatory neurological disorders which do not meet the criteria for CIDP. Specifically, case reports and cases series have indicated therapeutic responses to IVIG in autonomic neuropathies. (See Goodman, B. P. (2017). "Immunoresponsive Autonomic Neuropathy in Sjogren Syndrome-Case Series and Literature Review." Am J Ther doi: 10.1097/MJT.0000000000000583. and Oaklander, A. L. (2016). "Immunotherapy Prospects for Painful Small-fiber Sensory Neuropathies and Ganglionopathies." Neurotherapeutics **13**(1): 108-117).

Intravenous Albumin is approved for the treatment of hypovolemia (see attached package insert). The use of albumin to increase plasma volume in patients with POTS has been suggested. In this study, albumin will be used as an active control treatment to provide the same volume and protein load as IVIG but without the immunomodulatory effects.

Significance: There have been few well designed clinical therapy trials aimed at POTS patients and even fewer that are aimed at a particular pathophysiological subtype of POTS. Evidence suggests that POTS is a heterogeneous disorder with differing underlying mechanisms. Several uncontrolled case series have suggested a benefit of IVIG for POTS, but the volume expansion associated with infusion of IVIG make it difficult to assess the immunomodulatory effects of this treatment. We propose to evaluate the efficacy of IVIG using a double-blind randomized cross over design that will determine efficacy while reducing effects of inter-subject variability and placebo effect which are common problems in POTS therapy research. Even with the statistical advantages of a crossover design, the treatment cohort will be small, and this study is designed to be a pilot (phase II) study to evaluate the feasibility, tolerability and potential benefits of treatment. The results of this pilot study will provide the impetus and rationale for a larger multicenter clinical trial to definitively evaluate immunomodulatory treatment in POTS.

b. Current practice

Currently there are no pharmacological treatments for POTS that have proven efficacy in randomized controlled trials.

3. Study Design.

Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

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This will be a double-blind placebo controlled crossover study. See Schedule of study procedures below for time line:

Supplemental table D: Schedule of Study Procedures

	Screen	Baseline	Treatment versus Active Comparator (Albumin)																			Follow-up	
Study Weeks	-2	-1	0-4				5-7		9-11		12-17			17-20				22-24		26-28		30	32	34
Treatment #			1-4*				5-6		7-8		Washout			1-4				5-6		7-8		Final Visit		
Study day	-14	-7 to 0	0	7	14	21	35	49	63	77	91	105	118	119	126	133	140	154	168	182	196	210	224	238
Informed Consent	X																							
Medical History	X											X												
Vital signs, physician exam	X											X												
Inclusion/Exclusion Criteria	X	X										X	X											
Pregnancy Test[1]		X											X											
Autonomic testing[7]	X											X										X		
Pupillometry[7]	X											X										X		
Serological testing[7]	X											X										X		
Skin Biopsy[5]	X										X[6]											X[5]		
Supine and standing catecholamines	X										X	X										X		
Standing vitals	X	X					X				X	X	X					X				X		
VOSS	X	X									X	X	X									X		
ECG	X																							
COMPASS 31[8]	X	X									X	X	X									X	X	X
Quality of Life questionnaire (SF36)	X	X									X	X	X									X	X	X
Fatigue score	X	X									X	X	X									X	X	X
Symptom score	X	X									X	X	X									X	X	X
COMPASS-change				X		X	X	X	X	X	X		X		X		X	X	X	X	X	X		
Return daily diary[3]		X		X		X	X	X	X	X	X		X		X		X	X	X	X	X	X		X
Study Infusion			X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X			
Subject impression		X									X		X									X		X
Concomitant Medications		X									X		X									X		X
Adverse Events											X		X									X		X
Safety Labs (CBC/BMP)[4]	X							X			X		X						X			X		
Telephone call*												X											X	X

[1]. Serum or urine pregnancy test for women of childbearing potential

[2]. Blood testing includes: Complement C3/C4, quantitative immunoglobulins, gAChR, ANA, ENA, APLA, gliadin antibody, transglutaminase antibody, CRP

[3]. Daily diary will be picked up at every infusion

[4]. Safety labs: complete blood count (CBC) with differential, basic metabolic panel

[5]. Skin biopsy is not required. Results can be used if done within the last year. If no results available, PI discretion if biopsy is indicated.

[6]. Repeat skin biopsy assessment if needed can be done between 2-4 weeks after last infusion.

[7]. Within the past 12 months.

[8] Collected by online survey via RedCap

***Patients will follow structured exercise regimen, water and salt recommendations throughout 30 weeks**

***Infusion of study drug or albumin would occur on weeks 0, 1, 2, 3, 5, 7, 9, 11 (+/- 2 days) during part 1 and on weeks 17, 18, 19, 20, 22, 24, 26, 28 (+/- 2 days) during part 2. There will be a 6 week washout between weeks 11 and 17 and after week 28. Total study duration of 34 weeks**

Abbreviations: complete blood count (CBC), basic metabolic panel (BMP)

***Clinic visits are highlighted in grey and infusion visits are white**

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4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

As standard of care evaluation of POTS, patients will be evaluated with autonomic testing, pupillometry, supine and standing catecholamine levels, serological testing, and standing vitals. Skin biopsy (for determination of intraepidermal nerve fiber density) can be included at the discretion of PI in selected cases, Standard of care autonomic testing includes QSART testing, heart rate variability testing (via ECG), continuous blood pressure recording, Head Up Tilt Test, and pupil testing. Patients will also complete several surveys including COMPASS-31, Quality of Life questionnaire and fatigue symptom score.

Those patients with clinical features of autoimmunity will be eligible to enroll in the treatment study. Consenting patients will be assigned randomly to one of two groups. Both groups will receive both IVIG and albumin infusions (0.4 gm/kg). One group will receive IVIG infusions every week for 4 weeks then every 2 weeks for an additional 8 weeks (12 weeks total) followed by albumin infusions weekly for 4 weeks then every 2 weeks for 8 weeks (12 weeks total). There will be a 6 week washout and evaluation period between the treatment phases. The second group will receive albumin infusions first followed by IVIG infusions.

We will be following the Aston infusion center IVIG solution Infusion order. Patients will receive premedication's with 10mg of Cetirizine (Zyrtec) by mouth and 500 mg Acetaminophen (Tylenol) by mouth 30 min. (+/- 5 min) prior to infusion. After premedication and placement of peripheral IV, they will receive D5W 25 mL IV at 300 mL/hour (immediately before infusion). Then the patients will receive study medication in a blinded fashion. The dose of medication will be 0.4 g/kg (either Gammunex-C, 10% or Albumin, 10%). The dose will be rounded to the nearest 5 grams, and the dose will remain constant for each of the 8 study infusions even if weight changes. Since albumin is packaged at a 20% solution, this drug will be diluted to 10% using D5W prior to infusion. The prepared study drug dose will be provided by the research pharmacist in packaging marked with the study subject identifier and infusion number but will have no identifiers to indicate the drug identity (infusion nurse, patient and study coordinator must remain blinded to the treatment assignment). Infusion rate will start at 0.6 ml/kg/hour and may be increased by 0.6 ml/kg/hour every 15 min as, tolerated, to a maximum infusion rate of 210 ml/hour. Subsequent infusion rates may be started at the tolerated rate. Start and stop times and infusion rates will be recorded in the study log. Vital signs will be recorded at the start and end of the infusion and at the time of any changes of infusion rate or clinical symptoms. Once the study infusion is complete, the infusion nurse will alert the study coordinator, and the coordinator will check on the patient for any emergent AEs.

Post infusion, the intravenous catheter will be flushed with D5W 25 mL IV at 300 ml/hour and then the catheter will be removed. Once the coordinator check is complete the patient can be discharged.

Neither the patient nor the examiner will know if they are receiving IVIG or albumin until after the study is over. Patients in the study will be asked to complete a diary entry every day during the duration of the study (includes fluid intake, minutes of exercise, daily symptom score, and perceived side effects). More detailed assessment will be made at beginning, mid-point washout and end of study with including stand test, supine and standing catecholamine levels, COMPASS-31, fatigue score, quality of life score and symptom scores. Skin biopsy will be repeated at the assessment if the biopsy was performed at baseline and was abnormal.

Assessments will be made on days -1, 84, 111 and 196, with stand test, and supine and standing catecholamine levels. Symptom surveys COMPASS-31, Quality of Life questionnaire (SF-36), fatigue score, and symptoms score will be repeated at days -14, -1, 84, 98, 111, and 196. The VOSS score will be be performed at screening, baseline, all visits during the washout phase, and at final visit. The analysis will compare responses in the IVIG and placebo groups including individual comparisons between treatment and placebo and group comparisons. A specialized repeated measures analysis will be used to separate the effects of time, treatment and sequence of treatment in this cross-over design.

The primary outcome will be change in COMPASS-31 score (Sletten et al. 2012) (Rea, Campbell, and Cortez 2017). Because both treatments will expand plasma volume, we anticipate that both the IVIG and albumin groups will result in improvement in the COMPASS-31 orthostatic intolerance (OI) subscore. Accordingly, we will analyze the change in both the total COMPASS-31 scores and the score with the OI subscore removed.

Secondary outcomes will be patient subjective responses, reported activity level and objective measures including orthostatic tachycardia, supine and standing catecholamine profiles and skin biopsy results (nerve fiber density). The randomized crossover design will help reduce the confounding factors of interindividual symptom reporting variability and confounding effect of activity level on symptoms and drug carryover from phase 1 to phase 2 of the study. We will subsequently perform post hoc analysis comparing responders to non-responders to determine if baseline characteristics can identify subjects most likely to respond to this intervention.

Our statistician will plan to perform an interim analysis after the first 10 subjects have completed treatment.

The small sample size makes the study sensitive to patient drop out from intolerable side effects or inability to tolerate study design. Patient screening will include careful discussions of the importance of following study protocols. The study includes a 2 week baseline period during which the subjects will follow the study procedures related to daily diary entries to be certain that they are compliant.

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4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	IVIG infusions	☒ UTSW	☒ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes
2	albumin infusions	☒ UTSW	☒ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

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4.c. **Study Intervention #1** **IVIG Infusions**	
List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All Groups/Subjects because all subject will get IVIG while in the study	Volume expansion (felling less dizzy/lightheaded), more energetic, less fatigued, more stable heart rate, improve GI &urinary issue associated with POTS, and potential long term treatment for POTS

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

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4.c.
Study Intervention #1
Albumin infusions

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All Groups/Subjects because all subjects will get Albumin while in the study	Volume expansion (felling less dizzy, lightheaded, and fatigued)

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

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4.d. List ALL other research procedures or components not listed in table 4.b.
The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.

Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)

#	Research component • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Eligibility Assessments**			
	Medical History	1	1	
	VitalSigns/Physical Exam	1	1	
	Autonomic Testing	1	2	
	Skin Biopsy	1	2	
	Labs	1	5	
	Pregnancy test	0	2	
	Supine & Standing Catecholamines	1	3	
	QoL questionnaire	1	7	
	Compass Change score	0	16	
	COMPASS 31	1	7	
2	**Patient Responsibilities**			
	Daily Diary (Fluid & Exercise)	17		
	Symptom Score	0	8	
	Side effect form	0	8	
	Subject Impression Questionnaire	0	8	
3	**Insert component 3 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
4	**Insert component 4 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			

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5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Serious side effects of IVIG include renal dysfunction/failure, hemolysis, thrombosis, aseptic meningitis or allergic reaction. Common transient side effects include headache, fatigue, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling, flu like illness. Each infusion will include standard pre-medications with acetaminophen and cetirizine, and prn medications will be available for headache or nausea at each infusion.

Patients will be able to receive Ondansetron (Zofran) 4mg by mouth every 6 hours PRN for nausea or vomiting.

Vital signs will be taken prior to infusion, at each change of medication, at every rate increase, and at the end of the infusion medication.

All infusions will take place in the CRU infusion unit with experienced and qualified nurses.

Safety labs will be checked on weeks 2, 8, 15 and 24 and include complete blood count (CBC) and complete metabolic panel (CMP). If patient develops a serious side effect or intolerable and persistent common side effect during the treatment phase, infusion will be stopped and they will be considered a treatment failure for that part of the study. If this occurs during Part 1 of the cross-over treatment, these subjects will be allowed to start part 2 after week 12.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Physicians/PI will be available by pager 24/7 and on site during the research infusions. In the case of a serious side effect, subjects will be immediately directed to the appropriate nearest emergency facility.

If the subjects reports any of the following symptoms the infusion nurse will contact the coordinator. Nausea/vomiting, flushing, headache, lightheadedness, and dizziness. The coordinator will inform the PI.

If the subjects any of the following symptoms the infusion nurse will put the stop the infusion and contact the PI and coordinator for an immediate assessment. Chest pain, shortness of breath, swelling, angioedema, rash, any other signs of a serious reaction.

In the case of any unanticipated problems, the research pharmacist (who is unblinded to treatment allocations) may consult with Dr. Lauren Phillips (an autonomic disorders expert who is not involved with research assessments) who has agreed to serve as the safety officer for this study. Dr. Phillips will be responsible for review of abnormal safety labs or adverse events to determine if a patient should be withdrawn from the study for safety reasons.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

If yes, describe here