A study of subcutaneous immunoglobulin as chronic treatment for patients with chronic inflammatory demyelinating polyneuropathy

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BACKGROUND/RATIONALE

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune neurological disorder that causes limb weakness and numbness. Many patients require immunosuppressants and plasma exchange (PLEX) to control their symptoms. Intravenous immunoglobulin (IVIG) is also an effective treatment (Hughes et al, 2006 & 2008; Hughes, 2009; Cocito et al, 2010), and the American Academy of Neurology (AAN) guideline recommended that it should be offered in the long-term treatment of CIDP (Patwa et al, 2012). While effective, IVIG causes systemic side effects in about 5% of patients. These side effects include rash, pruritus, myalgia, fever, chills, headache, low back pain, nausea, vomiting, changes in blood pressure or heart rate, renal failure, and aseptic meningitis (Berger, 2008). For many patients who are chronically treated with IVIG, venous access may be a problem over time. An alternative is the subcutaneous (SC) route, which has been in use since 1980 for primary immune deficiency disorders and is the treatment of choice for this condition in Scandinavia and England (Radinsky et al, 2003). As compared to IV route, SC route maintains higher trough levels of immunoglobulins, increases patient independence, reduces systemic side-effects, and is better tolerated in those who are pregnant or sensitized to IgA (Radinsky et al, 2003). In a review of side effects associated with 33,168 SCIG infusions, no severe or anaphylactoid reactions occurred (Gardulf et al, 1995). Patients can self-administer medication, and hence, overall cost may be reduced. A retrospective study of 28 children with primary immunodeficiency in Canada showed that the mean difference in costs between IVIG and SCIG during the study period (1 year on IVIG and 1 year on SCIG) was $4,346 in favor of SCIG (Ducruet et al, 2011). Gardulf et al (1995) also reported a reduction of US$10,100 in cost per year per patient with SCIG use in Sweden. Similar cost savings were achieved in other countries as well (Lazzaro et al, 2014; Zbrozek, et al, 2014). Disadvantages of SCIG include more frequent infusions and local reactions at sites of infusion (transient swelling, soreness, redness, induration, local heat, and itching) in about 1% of patients.

There are few reports of SCIG used in patients with CIDP (Koller et al, 2006; Lee et al, 2008; Cocito et al, 2011). The data from these reports are summarized in table 1. In general, SCIG was well tolerated and had similar clinical effects as IVIG.

Table 1.Summary of reported use of SCIG in patients with CIDP.N/A = Data not reported; SE = side effects;

Pt No	Age	Gender	IVIG dose	IVIG Duration	SCIG dose	Response	SE of SCIG	Preference	Reference
1	N/A	N/A	60 g/mo	2 yrs	60 g/mo	Same as IVIG	None	SCIG	Cocito et al, 2011
2	N/A	N/A	70 g/mo	6 yrs	70 g/mo	Same as IVIG	None	SCIG	Cocito et al, 2011
3	N/A	N/A	50 g/mo	16 yrs	50 g/mo	Same as IVIG	None	SCIG	Cocito et al, 2011
4	N/A	N/A	60 g/mo	3 yrs	60 g/mo	Same as IVIG	None	IVIG	Cocito et al, 2011
5	N/A	N/A	80 g/mo	13 yrs	80 g/mo	Same as IVIG	None	SCIG	Cocito et al, 2011
6	73	F	60 g/mo	18 mo	16 g/wk (64 g/mo)	Stable course	Mild skin rxn	N/A	Lee et al, 2008
7	53	M	200 g once	One course	6.4 g/wk (25.6 g/mo)	Stable course ove	Mild swelling	N/A	Lee et al, 2008
8	45	M	N/A	< 2 yrs	0.4 g/kg/mo	Stable	None	SCIG	Koller et al, 2006

More recently, Markvardsen and colleagues (2013) reported the effect of SCIG in 30 CIDP patients characterized as IVIG-responders by their treating physicians (see also abstract by Jacobsen et al, 2012). The patients were randomized to receive either SCIG at a concentration of 1.6g/10cc or subcutaneous saline in a double-blinded fashion. Treatment with SCIG was demonstrated to be feasible, safe, and associated with improved strength, walking performance, and disability scores.

Despite the potential advantages in terms of cost and scheduling conveniences, there are inherent barriers to the transition from IV to SC routes of administration. First, self-administrating a large volume into the subcutaneous space may be unappealing to patients. Second, the limb weakness caused by the disease may make it difficult to prepare the solution, operate the pump, and inserting the needles. Third, many of the patients are elderly and may need considerable assistance to properly administer the medication. However, in

these patients, these obstacles may be overcome with assistance from a caregiver or a visiting nurse. In additions, the impacts on quality of life (QOL) have not been fully assessed in this subset of patients.

This study will survey the patients' barriers to the transition from IV to the SC route of administration. The results will form a basis for establishing a guideline for the use of SCIG.

SPECIFIC AIMS

As of October 2012, we identified more than 70 patients with the diagnosis of CIDP at the University of South Florida (USF) Neurology Clinic. We estimated that at least 2/3 of these patients meet the Inflammatory Neuropathy Cause and Treatment (INCAT) Group diagnostic criteria (Sander & Latov, 2003). Many of these patients still attend our clinic and many are dependent on IVIG to control symptoms. Data are lacking in terms of tolerability, although our physicians are often contacted by patients or infusion centers for guidance regarding treatment of Ig infusion related side effects such as hypertension, flu-like symptoms, headaches, and joint pain.

Specific Aim #1.This study will assess the QOL and adverse events experienced by patients on IVIG and whether patients currently treated with IVIG would be willing to try the SC route of administration. This specific aim will be achieved via telephone or face-to-face survey. The goal is to identify factors that may reduce the patients' willingness to consider alternate drug delivery method.

Specific Aim #2. For patients willing to switch to SCIG, this study will test the hypothesis that SCIG is safe and well tolerated and can be self-administered by patients with CIDP. We will monitor patients' adverse reactions via patient diary, questionnaires, examination, and laboratory studies.

Specific Aim #3. To test the hypothesis that SCIG is associated with better QOL, we will compare QOL measures pre- and post-treatment.

Specific Aim #4.We will collect clinical data to test the hypothesis that SCIG is efficacious in controlling the symptoms of CIDP. Patients will be followed with hand-held dynamometry (HHD) and 20-ft timed walk. Pre- and post-treatment scores will be compared using appropriate statistical analysis.

RESEARCH STRATEGY

SIGNIFICANCE:

We have a substantial number of CIDP patients who require frequent doses of IVIG. Due to the side effects and time required by the IV route, these patients would potentially benefit from SCIG for the reasons discussed. The purpose of this pilot study is to determine whether SCIG is well tolerated, can be self-administered, improves QOL, and is efficacious in controlling CIDP symptoms.

INNOVATION:

Currently, most if not all CIDP patients who required Ig treatment are receiving it via the IV route. If proven efficacious and better tolerated, SCIG would be an attractive alternative. Additional benefits of SCIG include lesser cost and increased convenience to patients.

APPROACH:

This is a prospective, open label study of SCIG for the treatment of patients with CIDP who are dependent on IVIG for control of symptoms.

Participants: Up to 30 patients with IVIG-dependent CIDP will be enrolled. To qualify, a patient must meet **ALL** of the inclusion criteria and **NONE** of the exclusion criteria.

Inclusion Criteria:

1) Confirmed diagnosis of CIDP (having 2 or more of the following):
    a) Weakness in any limb
    b) Motor fatigue significant enough to interfere with ADL's or work
    c) Paresthesia of sufficient severity to require medication
    d) Sensory impairment
    e) Walking impairment
2) Requires IVIG to control symptoms
3) Male or female patient, older than 18 years of age
4) Able to provide informed consent
5) Able to be trained to provide self-injection
6) Willing to be on birth control for the duration of the study (for women of reproductive potential)

Exclusion Criteria:

1) Thrombocytopenia or other bleeding disorders;
2) Patients on anticoagulation therapy with an INR > 3.5;
3) Severe or anaphylactoid reactions to IVIG;
4) Cancer (active or currently treated);
5) Pregnancy;
6) Breast-feeding;
7) Renal insufficiency (creatinine > 1.5 upper limit of normal) or failure;
8) Congestive heart failure;
9) Psychiatric illness that would interfere with ability to provide informed consent or adhere to protocol;
10) Current IVIG doses greater than 2 g/kg per month;
11) Subject with an IgA level < 5% lower limit of normal;
12) History of active infection with HIV, Hepatitis B or Hepatitis C;
13) Presence of any other medical condition, which in the opinion of the investigator might interfere with performance;
14) Participation in a trial of an investigational medicinal product for CIDP in the past 12 weeks.

Sample size and statistical analysis: Descriptive information for the rate of change, such as mean and standard deviation, will be calculated. Due to the small sample size and self-control used in this study, instead of using paired t-test, Wilcoxon paired ranked test will be used to compare the change of before and after from each patient. Significance level is defined as 0.05 and all of the analyses will be carried by SAS (version 9.2).

DESIGN: The study will be submitted to the USF IRB for approval.

Specific Aim #1. We will assess QOL using the Medical Outcome Study 36-item short form health status scale (SF-36) and the Rasch-built Overall Disability Scale (R-ODS). The scales have been validated in patients with CIDP (Merkies et al, 2002; van Nes et al, 2011). We will also do a survey of side effects and satisfaction with treatment (using the Treatment Satisfaction Questionnaire for Medication, or TSQM) and CIP-PRO20 scale (used by permission from Dr. Ted Burns; see appendix 3). No surveys will be completed until the patient signs the ICF. In addition, we will determine whether patients currently treated with IVIG would be willing to try the SC route of administration. Reasons cited for unwillingness to switch will be collected.

*Specific Aim #2.*To test the safety and tolerability of SCIG and feasibility of self-administration in patients with CIDP.

Patients will undergo baseline laboratory studies (CBC, CMP, TSH, quantitative IgG, PT/INR/PTT, pregnancy test for women of productive age), EKG, QOL questionnaires, treatment satisfaction and SE questionnaires, neurological and physical examination, and HHD measurements.

The study will provide all study medications, pumps, and supplies.

The first treatment of SCIG will start within 2 weeks after the last IVIG course (to maintain serum Ig levels). The first 2 weekly treatments will be done at USF Clinical Research Center (USF CRC). Patients will be trained to perform their own infusions during these initial sessions and will receive additional training sessions if needed. Subjects will start self-administration at home after they feel comfortable and confident with the procedure. For each weekly treatment, 20% solution of human normal IgG (Hizentra, CSL Behring AG) will be infused subcutaneously in the abdomen, flanks, arms, or thighs. Simultaneous SC infusion at multiple sites will be done using a multi-needle administration set. The volume at each infusion site will be 35 ml (7 g) or as tolerated, and administered via a syringe driver pump at a rate of 20-25 ml/hr/site or as tolerated. For this study, we will use a 1:1 conversion ratio for IV to SC dosing. The total SC dose weekly will be the patient's current IVIG dose divided by 4 (0.25 g/kg – 0.5 g/kg, corresponding to 1 – 2 g/kg per month, which is usually our maintenance dose for CIDP patients). Patients requiring > 2 g/kg of IVIG per month will be excluded from study. Weekly doses may be divided over the course of the week if needed (e.g., twice or three times a week). The SCIG will be given weekly for 24 weeks. The dosing will be individualized to each patient depending on dose and patient response. The regimen may be changed at any point as needed for patient comfort (e.g., a patient may increase his/her dosing schedule from 1 day to 2 or 3 days per week). After this period, the patients will be given a choice to discontinue treatment, continue with SCIG, or go back to IVIG. Pregnancy screen will be performed monthly on women with reproductive potential while they are undergoing treatment. If a subject becomes pregnant during the study, she will be withdrawn from treatment but will be monitored for the rest of the study. Please see table 2 for schedule of study visits. Study subjects will be monitored for allergic reactions (rash, urticaria, facial edema, wheezing, dyspnea, hypotension, and tachycardia) and injection site reactions (transient swelling, soreness, redness, induration, local heat, and itching) while receiving their first infusion at USF CRC. They will also keep a treatment log of injection site reactions for the duration of the study. Additional monitoring includes:

1. CBC with differential count and platelet count will be done prior to treatment and once per month during treatment.
2. Symptom monitoring will be done via phone and at scheduled visits at regular intervals. Study visits will have a window of +/- 7 days. Patients will have 24/7 access to investigators to report any symptoms that develop.
3. Subjects will be provided with emergency contact number for questions relating to any symptoms during the study.
4. In the event that the subject experiences a reaction at home, they will call us. They will also be trained to call 911 in an emergency situation.

Primary End-Points.

1. Significant side-effects requiring withdrawal from study.
2. Laboratory abnormalities requiring discontinuation of study.

Table 2. Schedule of Study Events and Visits.

	Screening	Day 1	Week 1	Week 2*	Week 3*	Week 4 (Month 1)	Week 8 (Month 2)	Week 12 (Month 3)	Week 16 (Month 4)	Week 20 (Month 5)	Week 24 EOS/ET (Month 6)	Follow-Up
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Informed Consent	x											
Inclusion/Exclusion Review	x	x										
Medical History	x	x	x									
Vital Signs Monitoring	x	x	x	x	x	x	x	x		x	x	
Physical/Neuro Exam	x	x	x			x	x	x	x	x	x	x
TSQM	x	x	x			x	x	x	x	x	x	
CIP-PRO20	x	x	x			x	x	x	x	x	x	
R-ODS	x	x	x			x	x	x	x	x	x	
SF-36	x	x	x			x	x	x	x	x	x	
Hand-held Dynamometry	x	x	x			x	x	x	x	x	x	
20-ft Timed Walk	x	x	x			x	x	x	x	x	x	
Electrocardiogram (ECG)	x											
PT/INR, PTT	x											
TSH	x											
Quantitative IgA, IgG, IgM	x	x				x	x	x	x	x	x	
Hematology, blood chemistry	x		x			x	x	x	x	x	x	x
Urine Pregnancy Test	x	x	x			x	x	x	x	x	x	
Subcutaneous Drug Administration Training		x	x	x	x							
Subcutaneous Drug Administration		x	x	x	x							
Drug Diary Training		x	x									
Drug Diary Review				x	x	x	x	x	x	x	x	
Drug Dispensation		x	x	x	x	x	x	x	x	x	x	
Drug Accountability							x	x	x	x	x	
* optional for additional administration training (can be completed at home)												

S*pecific Aim #3*. To test the hypothesis SCIG is associated with better QOL.

At baseline (pretreatment of SCIG, while subjects are being treated with IVIG), QOL and treatment satisfaction questionnaires (SF-36, CIP-PRO20, R-ODS, and TSQM) will be done. These measures will be repeated monthly during the course of the study. Data from pretreatment and treatment with SCIG phase will be compared using appropriate statistical methods with correction for multiple comparisons.

Specific Aim #4. To test the hypothesis that SCIG is efficacious in controlling the symptoms of CIDP.

Clinical response to SCIG will be monitored using HHD and 20-ft timed walk. Data from pretreatment and SCIG treatment phase will be compared. The HHD will measure force generated by the following muscle groups: Shoulder flexion, elbow flexion, elbow extension, wrist extension, first dorsal interosseous (hand), hip flexion, knee extension, knee flexion, ankle dorsiflexion. Measurement will be done bilaterally in duplicates. For the primary efficacy endpoint, HHD muscle strength measured at Week 24 will be compared to HHD muscle strength measured at baseline (pretreatment)

Secondary End-Point.

1. Progression of symptoms requiring reversion to IVIG, initiation of PLEX or other medications, or hospitalization.

Study Timeline and Feasibility: Participants will be recruited from the USF Neuromuscular Clinic. This Clinic is the tertiary referral center for the west coast of Florida, with a population of more than 4 million in the Tampa Bay region alone. We estimated that we have more than 70 patients with CIDP. In addition, we see an average of 2 new CIDP patients per month. Thus, there are enough patients for a 3 to 1 screening to enrollment ratio. Planned recruitment is an average of 1 patient every 1.5 months, for a total of 22.5 months. This schedule will place the final recruit completing the trial during month 30 and afford time during the final 6 months of the study for analyzing and preparing data for publication. This planned recruitment timeline is feasible given the size, established referral patterns, and historical recruitment experience of this clinic.

Rescue protocol: If a subject worsens (or "relapses") during the study, we will institute a rescue protocol. Relapse is defined as a 20% decrease in force (as detected on HHD) in more than 50% of the muscles tested when compared to baseline. In case of relapse, we will quantify the serum Ig levels, give IVIG 1 g/kg boost followed by SCIG at 2 g/kg per month. If the subject is already on 2 g/kg per month of SCIG, we will switch the patients back to IV administration and/or institute other treatment options (steroids, PLEX). Please see algorithm in Appendix 2. We will also switch back to IVIG if, at any point during the study:

a. The subject requests the switch due to treatment failure, adverse events or patient preference.
b. The investigators consider it to be in the best interest of the subject (i.e., due to intolerable side-effects, pregnancy, or noncompliance).

Potential Pitfalls and Alternative Strategies: There is the potential that some patients may lose interest or become too reticent in performing self-administration. Since compliance may be an issue with self-administration of an injectable medication, serum IgG levels will be done to monitor patient's adherence to protocol. The use of a home journal for recording therapy and a weekly telephone call will encourage compliance. In the scenario where there is concern with patient compliance, a weekly home therapy visit will be done. Attrition is also expected during the course of the study. If a participant becomes a 'drop out,' his or her data will be used in the analysis using an intention to treat protocol. Finally, while recruitment can be an issue in clinical trials, our planned enrollment rate of an average of 1 patient per 1.5 months is feasible. Furthermore, we already identified several patients who are appropriate for this trial. With an average of 2 new CIDP patients seen per month in the USF Neuromuscular Clinic, we should be able to recruit the remaining patients in the proposed timeline. Furthermore, there are many more CIDP patients in the greater Tampa region who are not being seen at USF. Thus, there is an untapped pool of subjects available. In the unanticipated scenario that we fall behind on subject recruitment, we have incorporated 6 additional months in our timeline for analysis and manuscript preparation that could be utilized for subject recruitment and treatment.

Data Management and Quality Control: Physiologic and questionnaire data will be collected across two time points (pre- and SCIG treatment phase) by the PI and coordinator who are all proficient in these testing methods. To ensure participant confidentiality, data will be coded to remove patient identifiers into a password-protected database (Excel) on a central computer system that is backed up daily. Data accuracy will be verified by double data entry. All original paper questionnaires will be locked in the PI's office with only coded identifying information. There will be an interim analysis done after 8 patients have completed the study.

Safety Monitoring and Adverse Events Reporting: Patients will be closely monitored for safety and any adverse events. This monitoring of treatment tolerability will be achieved through weekly telephone contact and monthly visit. During the study visits, subjects will be seen by a member of the research staff and will complete all study instruments, undergo clinical assessment, and have blood drawn for safety and compliance monitoring. At all study visits, concomitant medications, symptoms and side effects will be reviewed. Participants will also be provided with the Study Agent Intake and Symptom log which they will be required to complete. Adverse

Events will be reported to sponsor, USF IRB and regulatory agency, by investigators in a timely manner as required.

Dose and Toxicity Management:

A patient's treatment will be suspended in any of the following circumstances:

1. Allergic reaction to product
2. Request of patient or patient's physician;
3. Unusual symptoms reported during telephone follow-up or other unusual symptoms or blood work results observed during the study period
4. Pregnancy; or
5. Worsening symptoms requiring hospitalization or PLEX.

Any side effects associated or possibly associated with SCIG will be managed according to standard medical practice.

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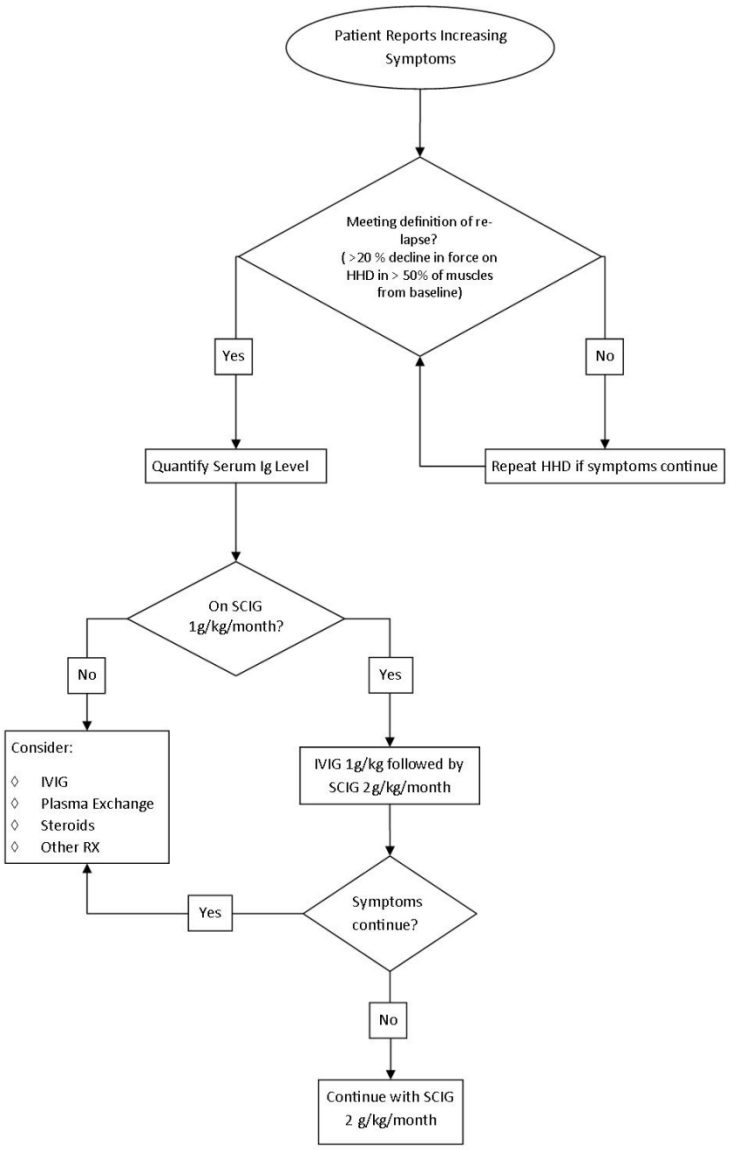
APPENDIX – 1

LIST OF ABBREVIATIONS

AAN	American Academy of Neurology
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CIP-PRO20	Chronic Immune-mediated Polyneuropathy – Patient Reported Outcome Scale
HHD	Hand-held Dynamometry
INCAT	Inflammatory Neuropathy Cause and Treatment
IVIG	Intravenous Immunoglobulins
PLEX	Plasma Exchange
QOL	Quality of Life
R-ODS	Rasch-built Overall Disability Scale
SC	Subcutaneous
SCIG	Subcutaneous Immunoglobulins
SE	Side Effects
SF-36	Medical Outcome Study 36-item Short Form Health Status Scale
TSQM	Treatment Satisfaction Questionnaire for Medication
USF	University of South Florida
USF CRC	USF Clinical Research Center

APPENDIX – 2

RELAPSE RESCUE PROTOCOL



APPENDIX – 3

CIP-PRO20 Scale 2014

Protocol: A Study of Subcutaneous Immunoglobulin as Chronic Tratment for Paitents with Chronic Inflammatory Demyelinating Polyneuropathy	**CIP-PRO**

Are you able to:	**0: Not at all**	**1: A little bit**	**2. A lot**
I am furstrated by my neuropathy.			
I am bothered by pain from neuropathy.			
I am off balance when walking because of my neuropathy.			
I have trouble getting dressed because of my neuropathy.			
I have trouble sleeping because of my neuropathy.			
I am bothered by limitations in performing my work (include work at home) because of my neuropathy.			
I have trouble driving because of my neuropathy.			
I am dependent on others because of my neuropathy.			
I am depressed about my neuropathy.			
I am falling because of my neuropathy.			
I am preoccupied with my neuropathy.			
I am unable to do all the leisure activities that I want to do because of my neuropathy.			
I am worn out because of my neuropathy.			
I have trouble eating because of my neuropathy.			
I have trouble doing activities around the house.			

Total Score: _____

Completed by: _____ Date: _____

APPENDIX 4

TSQM

TSQM *(Version II)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐0 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied

☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

APPENDIX 5

HAND HELD DYNAMOMETRY WORKSHEET

Protocol: A Study of Subcutaneous Immunoglobulin as Chronic Tratment for Paitents with Chronic Inflammatory Demyelinating Polyneuropathy	**HHD**

Not Tested	Muscle	Trial 1 (lbs.)	Trial 2 (lbs.)	Trial 3 (lbs.) *if needed*	Able to break? Yes	Able to break? No	If not tested, please explain:
☐	Left shoulder flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right shoulder flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left elbow flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right elbow flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left elbow extension				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right elbow extension				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left wrist extension				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right wrist extension				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left hip flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right hip flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left knee extension				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right knee extension				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left knee flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right knee flexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left ankle dorsiflexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right ankle dorsiflexion				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Left first dorsal interosseous				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____
☐	Right first dorsal interosseous				☐	☐	☐ Subject unable to perform task due to weakness ☐ Other (specify _____

Completed by: _____ Date: _____

APPENDIX 6

R-ODS Questionnaire

Protocol: A Study of Subcutaneous Immunoglobulin as Chronic Tratment for Paitents with Chronic Inflammatory Demyelinating Polyneuropathy	**R-ODS**

Are you able to:	**0: Impossible to perform**	**1: Performed with difficulty**	**2. Easily Performed**
Read a newspaper/book?			
Eat?			
Brush your teeth?			
Wash upper body?			
Sit on a toilet?			
Make a sandwich?			
Dress your upper body?			
Wash your lower body?			
Move a chair?			
Turn a key in a lock?			
Go to a general practitioner?			
Take a shower?			
Do the dishes?			
Do the shopping?			
Catch an object (e.g. ball)?			
Bend and pick up an object?			
Walk 1 flight of stairs?			
Travel by public transport?			
Walk and avoid obstacles?			
Walk outdoors < 1km?			
Carry and put down a heavy object?			
Dance?			
Stand for hours?			
Run?			

Total Score: _____

Completed by: _____ Date: _____

APPENDIX 7

Short Form-36 Questionnaire

Protocol: A Study of Subcutaneous Immunoglobulin as Chronic Tratment for Paitents with Chronic Inflammatory Demyelinating Polyneuropathy	**SF-36**

1. In general, would you say your health is:	□ 1 - Excellent □ 2 - Very good □ 3 - Good □ 4 - Fair □ 5 - Poor
2. Compared to one year ago, how would you rate your health in general now?	□ 1 - Much better than one year ago □ 2 - Somewhat better than one year ago □ 3 - About the same as one year ago □ 4 - Somewhat worse now than one year ago □ 5 - Much worse now than one year ago

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Response: 1 - Yes, limited a lot 2 - Yes, limited a little 3 - No, not limited at all		
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports.	□ 1	□ 2	□ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	□ 1	□ 2	□ 3
5. Lifting or carrying groceries	□ 1	□ 2	□ 3
6. Climbing **several** flights of stairs	□ 1	□ 2	□ 3
7. Climbing **one** flight of stairs	□ 1	□ 2	□ 3
8. Bending, kneeling or stooping	□ 1	□ 2	□ 3
9. Walking **more than a mile**	□ 1	□ 2	□ 3
10. Walking **several blocks**	□ 1	□ 2	□ 3
11. Walking **one block**	□ 1	□ 2	□ 3
12. Bathing or dressing yourself	□ 1	□ 2	□ 3

	Response:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**	1 - Yes	2 - No
13. Cut down on the amount of time you spent on work or other activities	□ 1	□ 2
14. Accomplished less than you would like	□ 1	□ 2
15. Were limited in the kind of work or other activities	□ 1	□ 2
16. had difficulty performing the work or other activities (took extra effort)	□ 1	□ 2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?	Response: 1 - Yes	2 - No
17. Cut down the **amount of time** you spent on work or other activities	□ 1	□ 2
18. **Accomplished less** than you would like	□ 1	□ 2
19. Didn't do work or other activities as **carefully** as usual	□ 1	□ 2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?	□ 1 - Not at all □ 2 - Slightly □ 3 - Moderately □ 4 - Quite a bit □ 5 - Extremely
21. How much bodily pain have you had during the past 4 weeks?	□ 1 - None □ 2 - Very Mild □ 3 - Mild □ 4 - Moderate

	□ 5 - Severe □ 6 - Very severe
22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	□ 1 - Not at all □ 2 - A little bit □ 3 - Moderately □ 4 - Quite a bit □ 5 - Extremely

These questions are about how your feel and how things have been with you during the past 4 weeks. For each question, please give the one answer than comes closest to the way you have been feeling, how much of the time during the past 4 weeks	Response: 1 - All of the time 2 - Most of the time 3 - A good bit of the time 4 - Some of the time 5 - A little of the time 6 -None of the time					
23. Did you feel full of pep?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
24. Have you been a very nervous person?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
26. Have you felt calm and peaceful?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
27. Did you have a lot of energy?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
28. Have you felt downhearted and blue?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
29. Did you feel worn out?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
30. Have you been a happy person?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6
31. Did you feel tired?	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	□ 1 - All of the time □ 2 - Most of the time □ 3 - Some of the time □ 4 - A little of the time □ 5 - None of the time

How TRUE or FALSE is each of the following statements for you?	Response: 1 - Definitely true 2 - Mostly true 3 - Don't know 4 - Mostly false 5 - Definitely false				
33. I seem to get sick a little easier than other people	□ 1	□ 2	□ 3	□ 4	□ 5
34. I am as healthy as anybody I know	□ 1	□ 2	□ 3	□ 4	□ 5
35. I expect my health to get worse	□ 1	□ 2	□ 3	□ 4	□ 5
36. My health is excellent.	□ 1	□ 2	□ 3	□ 4	□ 5

Total Score: _____

Completed by: _____ Date: _____