Study Title “The Efficacy Of Intravenous Immunoglobulin Therapy In Treatment Induced Neuropathy Of Diabetes”

NCT number: NCT02915263

Version 2.0

Document Date: Revised11/10/2016 (Original 9/10/2016)

# Protocol:

This study will be a double-blind, placebo-controlled pilot study of the effects of immune globulin (IVIG) on treatment induced neuropathy in diabetes. The goal of this pilot study is to obtain preliminary data on the magnitude of the treatment effect of IVIG on the neuropathic pain and neuropathy severity associated with TIND. The preliminary data will be used to power a larger treatment trial, and to aid our understanding of the mitigating factors in the treatment response.

The study will include a total 20 individuals. Subjects will be randomized equally to treatment or placebo. Treatment will consist of IVIG administered at 2 grams/kg divided over 2-4 days, with a follow up treatment 3 weeks (+/-3 days) later of IVIG 1gram/kg administered over 1 day.

***Subjects***: All individuals participating in the study will be recruited from Joslin Diabetes Center or Beth Israel Deaconess Medical Center from the clinical practice of Dr. Christopher Gibbons. Recruited subjects will review and sign the informed consent, undergo screening for eligibility:

***Inclusion Criteria:***

- Individuals with a diagnosis of diabetes and treatment induced neuropathy (defined by the onset of neuropathic pain within 8 weeks of a change in HbA1C exceeding 3 points over 3 months).
- Ages 18-60.
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***Exclusion Criteria:***

- No other known cause of neuropathy (chemotherapy, toxins, other medical disorder).
- Anticoagulation with warfarin, aspirin & Plavix together, or other anticoagulant that would place subjects at undue risk of bleeding from a skin biopsy. Aspirin or Plavix alone are not an exclusion criteria.
- Evidence of severe vascular disease (history of ulceration, poor wound healing, vascular claudication)
- Clinically active coronary artery or cerebrovascular disease
- History of allergic reaction to local anesthesia for skin biopsies or history of scarring or keloid formation.
- History of reaction to blood products or immune globulin.

***Screening Visit (Visit 1):*** Protocol Procedures- After signing an informed consent subjects will undergo the following:

1) Undergo a general physical examination, Pain VAS scores, pain questionnaires and SF-36.
2) Have a quantified neurological (neuropathy) examination using the Utah Early Neuropathy Score (UENS)(Singleton *et al.*, 2008).
3) Undergo autonomic testing (heart rate variability to paced breathing)(Gibbons and Freeman, 2004). Heart rate variability is measured over the course of 6 deep inspirations with the peak maximal average heart rates subtracted from the lowest heart rates during each breathing cycle.
4) Undergo a 3mm punch skin biopsy at the distal leg to investigate small sensory and autonomic innervation using standard methodology (Gibbons *et al.*, 2009, Wang and Gibbons, 2013). Outcome measures will include intra-epidermal nerve fiber density (IENFD).
5) Quantitative review of additional clinical outpatient data (renal function, retinopathy screening, laboratory studies).

***(Visit 2) Outpatient treatment 1***: IVIG 2 grams/kg over 2-5 days (to be administered within 28 days of screening visit).

SF-36 questionnaire.

Placebo would include administration of 0.1% albumin per day over 2-5 days.

***(Visit 3) Outpatient treatment 2***: IVIG 1 gram/kg over 1 day (to be administered 21±3 days after completion of initial treatment).

SF-36 Questionnaire.

Placebo would include administration of 0.1% albumin per day over 1 day.

***Visit 4:*** Follow up evaluation at BIDMC 28 +/- 3 days after 2nd IVIG treatment where they will undergo the following:

1) Undergo a general physical examination. Pain VAS scores, pain questionnaires and SF-36.
2) Have a quantified neurological (neuropathy) examination using the Utah Early Neuropathy Score (UENS)(Singleton *et al.*, 2008).
3) Undergo autonomic testing (heart rate variability to paced breathing)(Gibbons and Freeman, 2004). Heart rate variability is measured over the course of 6 deep inspirations with the peak maximal average heart rates subtracted from the lowest heart rates during each breathing cycle.
4) Undergo a 3mm punch skin biopsy at the distal leg to investigate small sensory and autonomic innervation using standard methodology (Gibbons *et al.*, 2009, Wang and Gibbons, 2013). Outcome measures will include intra-epidermal nerve fiber density (IENFD).
5) Quantitative review of additional clinical outpatient data (renal function, retinopathy screening, laboratory studies).

DOSING REGIMEN (Describe the subject or animal dosing)

***(Visit 2) Outpatient treatment 1***: IVIG 2 grams/kg over 2-5 days (to be administered within 28 days of screening visit).

Placebo would include administration of 0.1% albumin per day over 2-5 days.

***(Visit 3) Outpatient treatment 2***: IVIG 1 gram/kg over 1 day (to be administered 21±3 days after completion of initial treatment).

Placebo would include administration of 0.1% albumin per day over 1 day.

Selection of Placebo: The inclusion of placebo is critically important in a pilot study of this type in order to understand the potential treatment effects of IVIG on disease. Low dose albumin has been selected as the choice of placebo based on standard dosing from several other clinical trials of IVIG in different forms of neuropathy.

OBJECTIVES (Succinctly describe the major objectives for the overall proposed project)

To develop a therapeutic intervention for treatment induced neuropathy in diabetes. The primary endpoint will be to improve the pain associated with TIND, as well as improve nerve fiber structure (measured by biopsy analysis of IENFD) and by improvement in nerve fiber function.

Finally, we will improve our understanding of the potential mechanisms underlying this disorder, and define a potential plasma biomarker (elevated cytokines and inflammatory markers) that could identify patients that would respond to the treatment.

**Primary endpoint:**

The change in neuropathic pain severity and distribution between treatment and placebo groups between visit 1 and visit 2.

We expect that individuals with TIND treated with IVIG will have a >50% reduction in neuropathic pain and >30% reduction in the distribution of neuropathic pain 6 weeks after treatment. We expect that placebo that will have <20% reduction in neuropathic pain and no change in the distribution of neuropathic pain 6 weeks after treatment.

**Secondary Outcomes:**

The difference in quantified neurologic examination scores, biopsy scores and autonomic function between treatment and placebo groups at 6 weeks and 12 weeks.

We expect that individuals with TIND treated with IVIG will have improvements in quantified neurologic examination scores, autonomic function testing and nerve fiber density at follow up visits 4 and 5 compared to their initial visit. We expect that placebo treated individuals will have either no change or worsening of quantified neurologic examination scores, autonomic function testing and nerve fiber density at follow up visits 4 and 5 compared to their initial visit.

**Exploratory Outcomes:**

Exploratory outcome measures will include the effects of cytokine on neuropathic pain, small fiber neuropathy and autonomic neuropathy (heart rate variability).

# Statistical Analysis Plan

**Power calculations**:

This pilot study is being conducted in order to obtain adequate preliminary data for a larger clinical trial, but is powered to answer the primary endpoint analysis. Secondary endpoints and exploratory endpoints are not included in the power analysis

| Group | Change in pain score | Change in IENFD |
|---|---|---|
| Placebo | 2+/-2 | 0.5+/-1 |
| IVIG | 5+/-3 | 3+/-1.9 |

| | | |
|---|---|---|
| ***Number of pairs needed for 80% power to detect change.*** | ***10*** | ***7*** |

**Change in pain score calculation**: We are planning a study of a continuous response variable from matched pairs of study subjects. Prior data indicate that the difference in the pain response of matched pairs is normally distributed with standard deviation 3. If the true difference in the mean response of matched pairs is 3, we will need to study 10 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

**Change in IENFD score calculation**: We are planning a study of a continuous response variable from matched pairs of study subjects. Prior data indicate that the difference in the response of matched pairs is normally distributed with standard deviation 1.9. If the true difference in the mean response of matched pairs is 2.5, we will need to study 7 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Based on our preliminary data from the 4 subjects treated with IVIG, and the 104 untreated subjects with TIND, and the power analysis listed in Table 3, we calculate that 10 subjects in each of the treatment and placebo treated arms will provide >80% power with a 2 sided alpha of 0.05 to detect a difference between placebo and active treatment groups.

**A total of 20 subjects will be included in this study:**

1) IVIG treatment: Individuals with poorly controlled diabetes that have a sudden improvement in their HbA1C and the development of neuropathy (*meeting criteria for treatment induced neuropathy*). Subject number =10
2) Placebo Treatment: Individuals with poorly controlled diabetes that have a sudden improvement in their HbA1C and the development of neuropathy (*meeting criteria for treatment induced neuropathy*). Subject number =10.