FULL PROTOCOL TITLE
Topiramate as a disease modifying therapy for Cryptogenic Sensory Peripheral Neuropathy in Metabolic Syndrome (CSPN)

Protocol Version: 8.0
Protocol Date: 8/8/2018

SHORT PROTOCOL TITLE
The TopCSPN Study / Topiramate as a Disease Modifying Therapy for CSPN

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Supported by:
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IND Exempt (IND 125823)

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INVESTIGATOR AGREEMENT

I have read the foregoing protocol [*version 8.0, dated 8/8/2018]* and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by the NeuroNEXT Network in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents provided by the NeuroNEXT Network will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____ _____

Investigator Signature **Date**

_____

Print Investigator's Name

SIGNATURE PAGE

Study Number:

NN108

Principal Investigator Approval:

Signature: _____ Date: _____

Name: A. Gordon Smith, MD

NeuroNEXT Clinical Coordinating Center Approval:

Signature: _____ Date: _____

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NeuroNEXT Data Coordinating Center Approval:

Signature: _____ Date: _____

Name: Christopher Coffey, PhD

LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

6MWT	6 Minute Walk Test
ABC	Activities-specific Balance Confidence
AE	Adverse Event
ADA	American Diabetes Association
BMI	Body Mass Index
BMP	Basic Metabolic Panel
BPI-DN	Brief Pain Inventory – Diabetic Neuropathy
CCC	Clinical Coordination Center
CDE	Common Data Elements
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CRF	Case report form
CS	Clinically Significant
CSPN	Cryptogenic Sensory Peripheral Neuropathy
CSS PI	Clinical Study Site PI
C-SSRS	Columbia-Suicide Severity Rating Scale
DCC	Data Coordination Center
DOR	Delegation of Responsibility
DPP	Diabetes Prevention Program
DM	Data Management
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IENFD	Intraepidermal Nerve Fiber Density
IGT	Impaired Glucose Tolerance
IGTN	Impaired Glucose Tolerance Neuropathy
IMM	Independent Medical Monitor
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Nerve Conduction Studies
NCS	Not Clinically Significant
NINDS	National Institute of Neurological Disorders and Stroke
NQOL-DN	Norfolk Quality of Life – Diabetic Neuropathy
NIS-LL	Neuropathy Impairment Scale Lower Limb
NTSS-6	Neuropathy Total Symptom Score – 6
PPI	Protocol Principal Investigator
PLP	Paraformaldehyde Lysine Phosphate
PSC	Protocol Steering Committee

QOL	Quality of Life
QUICKI	Quantitative Insulin Sensitivity Check Index
RAPA	Rapid Assessment of Physical Activity
SAE	Serious adverse event
SD	Standard Deviation
SOA	Schedule of Activities
TUG	Timed Up and Go
UENS	Utah Early Neuropathy Scale

SYNOPSIS

Title: Topiramate as a Disease Modifying Therapy for Cryptogenic Sensory Peripheral Neuropathy in Metabolic Syndrome: The "TopCSPN Study"

Short Title: The TopCSPN Study

Primary Objective: Determine if oral topiramate slows progression of CSPN using intraepidermal nerve fiber density (IENFD) as a primary measure of axon loss and the Norfolk Quality of Life – Diabetic Neuropathy (NQOL-DN) as a measure of neuropathy related quality of Life.

Secondary Objective: Determine the patient focused clinical relevance of change in IENFD and other CSPN surrogate measures using measures of pain, QOL, balance and mobility.

Design and Outcomes: The TopCSPN study will consist of screening and baseline visits, safety and monitoring visits every 16 weeks, evaluation visits at 32 and 64 weeks, a 96-week end-of-treatment visit, and a final safety assessment visit following termination of study drug. Distal thigh IENFD and the NQOL-DN will serve as co-primary outcome measures.

Interventions and Duration: The proposed study is a 96-week double blind randomized placebo-controlled trial of topiramate at a target dose of 100 mg daily (50 mg twice daily) as a potentially disease modifying therapy for cryptogenic sensory peripheral neuropathy (CSPN). Randomized participants will return to the clinic for follow up visits every 16 weeks. Evaluation visits will occur at 0, 32, 64 and 96 weeks. Enrollment will occur over a 48-week period. Dropout is estimated to be 4% at 32 weeks, 8% at 64 weeks, and 12% at 96 weeks.

Sample Size and Population: After a screening period, a total of 125 male and female participants from 18 to 80 years of age, inclusive, will be enrolled into two treatment arms (topiramate 100 mg daily or matching placebo). Enrollment will be stratified by body mass index (BMI).

1. STUDY OBJECTIVES

1.1. Primary Objectives

The primary objective of this study is to determine if oral topiramate slows neuropathy progression and improves patient relevant outcomes. Change in Intraepidermal Nerve Fiber Density (IENFD) and in the validated Norfolk Quality of Life-Diabetic Neuropathy (NQOL-DN) scale will serve as co-primary endpoints. The study will be considered positive if there is significant treatment effect for both, or efficacy in one and noninferiority in the other (see the Go/No-Go section for details of the predefined algorithm).

The primary objective is to determine if topiramate alters the natural history of progressive decline in Intraepidermal Nerve Fiber Density (IENFD) and improves neuropathy related quality of life. A positive signal for both primary outcome measures (Intraepidermal Nerve Fiber Density and Norfolk Quality of Life-Diabetic Neuropathy) would support additional study.
Lack of improvement in either IENFD or NQOL-DN would indicate a Phase III trial of topiramate

as either a disease modifying or symptomatic agent for Cryptogenic Sensory Peripheral Neuropathy (CSPN) was not warranted. A predefined detailed Go-No Go algorithm is provided in the statistical methods section. If there is treatment efficacy in one endpoint and noninferiority in the other the trial will be considered possible.

Pain, falls and reduced mobility due to distal sensory nerve injury reduce quality of life (QOL) in patients with Cryptogenic Sensory Peripheral Neuropathy (CSPN). The 47-item Norfolk Quality of Life –Diabetic Neuropathy (NQOL-DN) Scale is a validated neuropathy specific patient reported outcome measure developed following 1,000 structured patient interviews. The scale includes small fiber, large fiber, autonomic, symptoms, and activities of daily living subscores[27]. The scale has been translated into 10 languages including Spanish[40]. The NQOL-DN captures symptoms related to diabetic neuropathy, which are in turn very similar to those experienced by CSPN patients. The NQOL-DN is responsive to change and significantly correlates with other clinical and confirmatory measures of neuropathy[27] and has shown utility in both diabetic and familial amyloid polyneuropathy related to transthyretin mutations[41]. The mean total NQOL-DN among 379 American and European patients with mild diabetic neuropathy was 27.3. However, many patients with diabetes who do not have neuropathy answered affirmatively to a number of the general QOL questions. Therefore, the NQOL-DN score for patients with moderate CSPN are expected to be much lower. Inclusion criteria will require a NQOL-DN score of >9 in order to ensure some degree of baseline neuropathy related disability.[28] This cutoff was selected following discussions with the scale's developer.

Cryptogenic Sensory Peripheral Neuropathy (CSPN) is clinically characterized by early injury to small unmyelinated axons, resulting in denervation of the epidermis (reflected in reduced Intraepidermal Nerve Fiber Density (IENFD) and positive sensory symptoms including pain. Measures of small fiber function typically decline before those reflecting large fibers[42]. These features make IENFD an appropriate objective measure of change in peripheral nerve integrity. IENFD is more sensitive than quantitative sensory testing or nerve conduction studies (NCS) in detection of idiopathic [43] and diabetic and prediabetic neuropathy[10,44]. IENFD is responsive to treatment and shows at least transient improvement with exercise intervention in patients with neuropathy associated with both diabetes and metabolic syndrome[10,11].

1.2. Secondary Objectives

The secondary aim is to evaluate clinical meaning of change in Intraepidermal Nerve Fiber Density (IENFD), and examine the relative contribution of its change to improvement in clinically meaningful outcomes.

2. BACKGROUND

2.1. Target Population

The target population is patients with Cryptogenic Sensory Peripheral Neuropathy (CSPN), also commonly referred to as idiopathic neuropathy. Between 1/3 and 1/2 of patients with distal

symmetric polyneuropathy have no identifiable cause for neuropathy on detailed laboratory evaluation[3,63]. As summarized in sections 2.3 and 2.4 there is an expanding body of data linking obesity and its metabolic consequences to CSPN risk. Insulin resistance and glucose intolerance are present in up to 50% of CSPN patients[2]. Metabolic syndrome (defined as three of the following: prediabetes/diabetes, central obesity, low HDL, elevated triglycerides, and hypertension) is observed in >80% of patients with CSPN with IGT, and over 50% of those with normal glucose tolerance.

2.2. Study Timeline

Once enrollment begins, the study will take approximately four years to complete. A lead-in period of 32 weeks will be followed by the recruitment phase. Recruitment is anticipated to take 48 weeks from first subject enrolled. A total of 125 subjects will be randomized into the study. All subjects will be followed for 96 weeks. The last subject visit is anticipated to occur approximately 144 weeks after first subject enrolled. Data cleaning and analysis will be completed within 16 weeks following study closure.

2.3. Rationale

Peripheral neuropathy affects >10% of those over 40 years old [1], approximately half of whom have cryptogenic sensory peripheral neuropathy (CSPN), resulting in reduced quality of life (QOL) due to pain, sensory loss, imbalance, and fall related injuries. CSPN is a significant cause of patient morbidity, for which there exists no disease modifying therapy. Clinically similar to early diabetic neuropathy, it is characterized by preferential injury to small axons, and frequently results in prominent sensory loss and neuropathic pain. While the precise etiology of CSPN is unknown, and likely multifactorial, accumulating evidence indicates that obesity, dyslipidemia, and insulin resistance/prediabetes (metabolic syndrome) are linked to CSPN risk[2]. Patients with CSPN have an elevated risk of metabolic syndrome[3,4] and patients with prediabetes have an elevated risk of CSPN[5]. Obesity and dyslipidemia also significantly increase the risk of neuropathy among diabetic patients[6]. Animal models support the hypothesis that obesity and prediabetic levels of glucose dysregulation cause neuropathy[7-9].

Our previous studies show that exercise improves nerve regenerative capacity, results in increased intraepidermal nerve fiber density (IENFD) and improves pain among patients with CSPN and prediabetes [10]. Together, these findings suggest CSPN is potentially reversible. However, lifestyle interventions are clinically limited by noncompliance and poor sustainability. While randomized clinical trials of strategies to treat metabolic syndrome in CSPN are lacking, the available data suggest aggressive management of metabolic syndrome components may be effective. The NINDS funded Impaired Glucose Tolerance Neuropathy (IGTN) study demonstrated that one year of diet counseling and exercise based on the protocol used in the Diabetes Prevention Program (DPP) resulted in improved IENFD and reduced pain among patients with CSPN and impaired glucose tolerance (IGT)[10]. A similar study in patients with diabetic neuropathy found consistent results[11]. The Steno-2 trial demonstrated that aggressive management of metabolic syndrome features resulted in a significantly reduced risk of autonomic

neuropathy compared to those treated conventionally[12]. There was no impact on vibration sensation assessed using a biothesiometer, suggesting particularly robust therapeutic benefit for small diameter axons (the fiber population for which topiramate has shown promise). Our preliminary data indicate aggressive exercise results in enhanced peripheral nerve regeneration capacity in metabolic syndrome patients. Cumulatively, these data support the hypothesis that metabolic syndrome is linked to CSPN risk, and that aggressive management may be an effective strategy to enhance nerve regeneration and improve patient symptoms. However, currently available lifestyle interventions are very difficult to employ in a clinical setting due to poor compliance and attrition from the necessary behavioral changes. Development of better pharmacologic approaches is a major priority.

2.4. Supporting Data

Topiramate is a promising therapeutic approach to CSPN. Clinical trials of this anticonvulsant agent in diabetic neuropathy suggest improvement in pain and QOL, but also in measures of peripheral nerve function including sensory testing and IENFD.[13]. Topiramate has multiple potentially neuroprotective effects, including sodium channel inhibition, increased insulin sensitivity, and significant weight loss, which is greatest among obese patients [14,15]. It has been extensively studied for the treatment of epilepsy and migraine and is generally safe and well tolerated. Several studies suggest a potential benefit for neuropathic pain associated with diabetic neuropathy. The CAPSS-141 study enrolled 323 patients with painful neuropathy and found a significant improvement in pain severity, with a 50% response rate (>30% pain reduction) over 12 weeks compared to 34% for placebo ($p<0.004$)[16]. A 26-week open label extension study involving 225 participants demonstrated a durable treatment benefit[17,18]. Three studies with similar design[19,20], failed to demonstrate pain efficacy, but were limited by a high placebo response rate and use of a less specific visual analog pain outcome measure [21]. Small studies suggest topiramate therapy not only results in improved pain, but also improves QOL and preferentially impacts measures of small fiber function, including an increase in IENFD[22,23]. Data from animal models of diabetes also support its potential therapeutic efficacy[24,25]. We hypothesize that topiramate will significantly slow the natural history of IENFD decline and will improve neuropathy specific QOL in patients with CSPN.

Topiramate has multiple potential therapeutic mechanisms relevant to neuropathy. It is associated with significant weight loss that may result in improved insulin resistance and reduction of overall metabolic risk for neuropathy. There are currently 5 drugs available in the United States for long-term weight loss: orlistat, lorcaserin, phentermine-topiramate (Qysmia), naltrexone-buproprion and liraglutide. Mean weight loss varies from 4-9%, with phentermine-topiramate generally demonstrating the highest mean weight loss (8.6-9.3%), with 70% of treated patients experiencing >10% weight loss[26]. Topiramate monotherapy is associated with weight loss on par with other approved weight loss medications and greater than that observed in the IGTN Study and other studies of exercise and diet for neuropathy. Obese diabetic patients treated with topiramate alone lost 6.6% of body weight over 11 months, most of which was lost in the first 5 (5.5%) [27,28]. A recent meta-analysis of topiramate trials found an average weight loss of 5.34 kg

among 3320 individuals (6.58 kg for those treated > 28 weeks)[21]. The CAPSS-141 study of topiramate for diabetic neuropathy demonstrated a 2.6 kg weight loss over 12 weeks[22], and a 5.2 kg weight loss over 38 weeks in the open label extension[23]. Weight loss was greatest in obese individuals. Among 38 epilepsy patients treated with topiramate, there was a mean weight loss of 7.3% at one year. Among those with a BMI of $\geq$30 kg/m^2 the one-year weight loss was 11%. Weight loss at 3 months was associated with reduced caloric intake. Afterwards, caloric intake returned to normal but weight loss continued, and ultimate weight loss was correlated with loss of body fat mass. These data suggest weight loss is due to additional mechanisms other than appetite suppression[29]. Topiramate leads to weight loss and reduced adiposity in rodent models and humans via decreased food intake and energy expenditure that is mediated by improved insulin and leptin signaling at the hypothalamic level[30]. Multiple studies demonstrate that topiramate improves insulin sensitivity independent of its weight loss effects[30-32]. Data from a high fat fed mouse model indicate improved insulin sensitivity is driven by uptake in adipose tissue, and blocked by intravenous tolbutamide, suggesting central nervous system uptake is necessary for this metabolic benefit[19]. In a high fat fed rat model, topiramate's insulin sensitizing effects were in part mediated at the hepatic level by modulation of insulin receptor isoforms, increased adiponectin production and receptor expression, and lower TNF α levels[20]. As with neuropathy, animal models support its potential efficacy as a weight loss therapy, and also demonstrated improvement in insulin sensitivity that may be independent of weight loss effects[30-33].

Beyond improvement in weight and obesity-related metabolic consequences, topiramate inhibits voltage-gated sodium and calcium channels[22,34]. There is evolving data linking changes in voltage-gated sodium channel function to CSPN, including a recent report of a high prevalence of SCN9A sequence variants in patients with otherwise idiopathic isolated small fiber involvement[14,17]. In these patients, with prominent neuropathic pain, sodium channel mutation leads to increased sensory axon irritability, suggesting a pharmacological role for sodium channel inhibition. It is likely that analogous acquired altered sodium channel function is linked to other forms of neuropathy, including diabetic and chemotherapy induced neuropathies[35-37]. Alterations in cellular excitability may both increase pain and lead to axon loss and progressive neuropathy[38]. Development of a well-tolerated small molecule approach to blockade of voltage gated sodium channels is a priority. Topiramate has been shown to reduce peripheral nerve excitability, likely via inhibition of voltage gated sodium channels[34,39]. While topiramate has multiple potential mechanisms of action (weight loss, improved insulin sensitivity, sodium channel modulation), the fact that each would be expected to have potential benefit in CSPN supports its further evaluation as a disease modifying therapy.

While topiramate doses used in diabetic neuropathy trials have varied from 100-400 mg daily, data from two small trials suggest 100 mg/day is associated with improvement in both IENFD and neuropathy specific QOL assessed using the Norfolk Quality of Life –Diabetic Neuropathy (NQOL-DN) scale.[24,25]. Doses above 100mg daily are more likely to be associated with neuro-cognitive side effects. A Cochrane review of the use of topiramate for headache suggests there is no

additional benefit to doses over 100 mg daily. In light of the greater risk of side effects at doses over 100 mg daily, these data support selection of the 100 mg/day target dose.

3. STUDY DESIGN

This is a 96-week double blind randomized placebo-controlled trial of topiramate at a target dose of 100 mg daily (50 mg twice daily) as a potentially disease modifying therapy for CSPN. After a screening period, a total of 125 male and female subjects from 18 to 80 years of age, inclusive, will be enrolled into two treatment arms (topiramate 100 mg daily or matching placebo). Randomized subjects will return to the clinic for follow up visits on a regular basis. Enrollment will occur over a 48-week period. All subjects will be followed for 96 weeks.

The study will consist of screening and baseline visits, safety and monitoring visits every 16 weeks, evaluation visits at 32, 64, and 96 weeks, and a final safety assessment visit following termination of study drug. The figure below displays the anticipated recruitment schedule and number of evaluable subjects at each visit, accounting for 12% dropout over 96 weeks. A Schedule of Assessments associated with each visit is provided at the end of the protocol in Appendix A.

TopCSPN Visit Schedule

Months	0-6	7-10	11-14	15-18	19-22	23-26	27-30	31-34	35-38	39-42	43-48	Total
Screening		62	62	62								186
Baseline		***41***	***42***	***42***								***125***
Week 16			41	42	42							125
Week 32				***40***	***40***	***40***						***120***
Week 48					40	40	40					120
Week 64						***38***	***38***	***39***				***115***
Week 80							38	38	39			115
Week 96								***36***	***37***	***37***		***110***
Total Safety Monitoring		0	41	42	82	40	78	38	39	0	***NA***	***360***
Total Evaluation		41	42	82	40	78	38	75	37	37	***NA***	***470***

Assumptions:
(1) One in three screened potential participants will fail screening
(2) Participant attrition will be 4% at 8 month of follow-up, 8% at 16, and 12% at 24 month study completion

Participants will be seen for a screening visit, of which up to 30 days will be allotted to complete the screening assessments. After informed consent is obtained, the investigator will review inclusion/exclusion criteria with the participant, obtain a medical, family, and neurological history and perform a general medical and detailed neuromuscular physical examination including vital signs. Concomitant medications, including all nutritional, herbal and alternative therapies, will be recorded.

After meeting all entry criteria, participants who continue to meet all inclusion/exclusion criteria after screening will present to the clinic for the baseline visit. The baseline visit will be performed within 30 days of the screening visit. *However*, the investigator will review, date and initial the screening laboratory assessments to confirm participant eligibility for study participation prior to the baseline visit procedures. Therefore, adequate time must be provided for the laboratory results to be received from the central laboratory. The investigator or designee will again review the study inclusion/exclusion criteria and participant medical history, confirming that the participant meets criteria for study participation before randomization.

Participants will be seen for safety and follow-up visits at 16, 48 and 80 weeks following the baseline visit. Participants will be seen for evaluation visits at 32, 64 and 96 weeks. All tests listed for the quarterly monitoring visits will be performed at each of these visits in addition to NCS, distal thigh skin biopsy for IENFD, functional and mobility testing, laboratory monitoring for metabolic status (fasting insulin and glucose, fasting lipid panel, hemoglobin A1c). The final study treatment visit will occur 96 weeks following baseline. All assessments performed at the evaluation visits will take place. The investigator will perform a complete physical examination. All study drug and study drug packages will be collected from the participant at this visit and a final assessment of study drug compliance will be calculated. A final safety visit will occur by telephone, or in person at the discretion of the site PI, 4 weeks (± 7 days) following the last dose of study drug.

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1. Inclusion Criteria

1. Age 18-80
2. Diagnosis of confirmed cryptogenic symptomatic distal symmetric peripheral polyneuropathy based on the Toronto consensus criteria for probable neuropathy (the presence of ***unequivocal*** signs and symptoms of neuropathy)[45].
3. Evidence of symptomatic neuropathy based on a screening visit NQOL-DN score of >9
4. Metabolic syndrome based on modified ATPIII criteria, with a BMI ≥ 25 kg/m^2 [46] . Specific criteria require 3 of the following 6 to be present at the screening visit.
    - Waist circumference >102 cm for men, >88 cm for women
    - Serum triglycerides of ≥ 150 mg/dl
    - HDL < 40 mg/dl for men, < 50 mg/dl for women
    - Those with either a normal HDL or TRG who are taking a lipid lowering medication for this purpose.
    - Blood pressure ≥ 130/85 mm Hg or use of anti-hypertension drug
    - Prediabetes based on American Diabetes Association (ADA) criteria at screening based on any one or more of the following: fasting plasma glucose - 100 mg/dL to 125 mg/dL (5.6 mmol/L to 6.9 mmol/L),
      2-hour glucose tolerance test - 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0

mmol/L), or hemoglobin A1c between 5.7% and 6.4%.

5. No current or prior history of therapy with topiramate.
6. If female of child-bearing potential (i.e., not surgically sterile or post-menopausal defined as age > 51 years without menses for ≥ 2 years), negative serum pregnancy test at screening and negative urine pregnancy test at baseline visit.
7. Women of child-bearing potential or men with sexual partners of childbearing potential be willing to use an acceptable method of birth control for the duration of the study and for 12 weeks following completion of study drug therapy. Acceptable methods of birth control include abstinence, oral contraceptives, the contraceptive patch, intra-uterine device, the contraceptive ring, and or barrier contraception such as condoms with spermicide.

4.2. Exclusion Criteria

1. CSS-PI clinical determination of an alternative cause for peripheral neuropathy (including but not limited to rheumatological disorders, Hepatitis B or C, Breast Cancer treated with neurotoxic chemotherapy within the past 15 years). All potential subjects will have screening neuropathy labs including assessment for diabetes (Hemoglobin A1c, oral glucose tolerance test), vitamin B12 level, and immunofixation[47].
2. Diagnosis of diabetes by history, or screening laboratory results including: HgA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), or 2-hour oral glucose tolerance ≥ 200 mg/dL (11.1 mmol/L). Borderline screening labs can be repeated within two weeks with PPI approval.
3. History of recurrent nephrolithiasis, a single episode of nephrolithiasis within one year prior to screening, or use of ongoing preventative treatment.
4. Family history of a hereditary neuropathy in a first-degree relative.
5. Severe neuropathy: Utah Early Neuropathy Score > 24 at screening
6. Active foot ulceration or a history of a nontraumatic foot amputation.
7. ECG with QTc more than 450 ms in men, or 470 ms in women.
8. Current or planned therapeutic anticoagulation including coumadin or oral factor X or thrombin inhibitor therapy (anti-platelet agents are permissible).
9. Chronic corticosteroid use excluding topical or inhaled treatment.
10. Use of a carbonic anhydrase inhibitor (such as acetazolamide) due to risk of nephrolithiasis.
11. Planned bariatric surgery
12. Use of other weight loss medications.
13. Use of scheduled opiates, or as needed opiate medications more than three times weekly.
14. Use of topical capsaicin products within 16 weeks of screening or at any time on study.
15. Medication change for neuropathy symptoms during the 8 weeks prior to screening; or anticipated change for the duration of study participation.
16. Current use of an intrathecal pain pump or spinal cord stimulator.
17. Screening laboratory creatinine ≥ 2.0 mg/dl.
18. Severe edema, dermatologic or lower extremity condition that would increase risk of skin biopsy.

19. Major depression, bipolar affective disorder, or other mental health disorders that are sufficiently severe to increase adverse event risk or impact neuropathy assessment in the opinion of the responsible site principal investigator.
20. Current suicidal ideation within one year prior to the baseline visit as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS).
21. Ataxia sufficiently severe to represent an unacceptable fall risk in the opinion of the site principal investigator.
22. A serious medical condition expected to dramatically shorten life span or prevent participation.
23. Any clinically significant condition or illness, which, in the opinion of the CSS-PI, would pose a risk to the subject or might confound the study including metabolic acidosis, bone marrow suppression, blood dyscrasias, bleeding disorder, or closed angle glaucoma.
24. History of alcohol or drug abuse within the past two years, or existing neuropathy related to past drug or alcohol abuse.
25. History of malignancy within five years prior to study enrollment, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer.
26. A history of epilepsy.
27. An inability to understand or cooperate with the procedures of the study.
28. Pregnant, or intending to become pregnant, or breastfeeding.

ADA Diagnostic Criteria for Diabetes and Prediabetes

Diagnosis	Fasting Plasma Glucose	2-Hour Oral Glucose Tolerance Test	Hemoglobin A_{1C}
Normal	< 100 mg/dL (5.6 mmol/L)	< 140 mg/dL (7.8 mmol/L)	< 5.7%
Prediabetes	100 mg/dL to 125 mg/dL (5.6 mmol/L to 6.9 mmol/L)	140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L)	5.7% to 6.4%
Diabetes *(excluded)*	≥ 126 mg/dL (7.0 mmol/L)	≥ 200 mg/dL (11.1 mmol/L)	≥ 6.5%

4.3. Subject Withdrawal Criteria

A subject may discontinue study drug or withdraw from study participation at any time without bias for any of the following reasons:

Administrative

1. Withdrawal of consent by subject
2. Request of Study Sponsor or Principal Investigator
3. Request of primary care physician
4. Pregnancy (must stop study drug)

5. Subject deemed lost to follow up/failure to return
6. Early termination of study
7. Other

Adverse Event

1. Worsening of the disease under study
2. Worsening of pre-existing disease (other than disease under study)
3. Intercurrent illness
4. Death
5. Major/clinically significant alteration in laboratory values after beginning study drug
6. Prolonged QTc
7. Active suicidal Ideation based on the C-SSRS
8. Other adverse event

4.4. Study Enrollment Procedures

Subjects will be recruited from 14 NeuroNEXT sites and 1 non-NN site in the United States. Investigators will be responsible for obtaining written consent from each potential subject after adequate explanation of the purpose, study procedures, and any risks associated with the study.

Treatment for each subject will be assigned by a randomized code. A block randomization scheme will be used to ensure approximately even distribution of subjects in treatment groups for each BMI strata.

4.4.1. Subject Recruitment and Retention

Subjects will be recruited from clinics at participating NeuroNEXT Network sites. Postings will be placed on selected website(s). Flyers about the study will be sent to community neurologists at NeuroNEXT clinical sites. Webinars will be conducted for subject recruitment as needed. Interested subjects will be contacted by the investigators or their staff and invited to participate. These recruitment strategies will include a mechanism by which the patients can provide their contact information. We will use the NeuroNEXT Recruitment and Retention Committee to identify recruitment strategies.

4.4.2. Screening Logs

All clinical sites will maintain screening logs documenting demographic information including age, gender, race and ethnicity, reasons for ineligibility at the screening visit, and reasons for non-participation if eligible.

Screening logs to document demographic information and reasons for ineligibility and non-participation will be stored centrally at the NeuroNEXT Data Coordination Center. Information about screening failures and successes will be compiled and reviewed on a periodic basis so that feedback can be provided to sites.

Screening log data will be provided to the study team, de-identified and analyzed to determine the most successful routes for information dissemination and recruitment strategies for ongoing recruitment in this study and for future studies. The study team will work to identify any common reasons for screen failure that might be identified to consider amendments to the study to adjust inclusion/exclusion criteria if a large number of patients are screen failing for specific reasons that would not ultimately affect the study results if allowed. Likewise, reasons for non-enrollment will be tracked centrally. If there are recurring themes adjustments will be attempted to target this problem, as long as the adjustments do not affect the study conduct or data quality.

4.4.3. Informed Consent

Written informed consent will be obtained from each study participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form approved by the NeuroNEXT Central Institutional Review Board (CIRB), which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and a copy will be given to the participant. It will also be explained to the participant that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

Informed consent will be obtained by licensed physician investigators only, who are trained on the study and delegated appropriately as being authorized to obtain consent. The site PI will typically be involved in explaining the study and will play a role during the consent process and answering any questions in conjunction with the coordinator, as well as overseeing that the process is carried out correctly.

Optional DNA and tissue banking is planned for future research. Participants will consent to their preference for banking DNA and tissue separately.

4.4.4. Assent

Children (age less than 18) will not be allowed to participate in this study.

4.4.5. Randomization/Treatment Assignment

Randomization to study treatment (either topiramate or matching over- encapsulated placebo) will occur using an interactive web response system (IWRS). Online randomization will follow confirmation of eligibility and completion of all required baseline procedures. Randomization codes will be constructed using random permuted blocks to assure balanced randomization over time with stratification by BMI. BMI of 30.0 will serve as stratification cutoffs reflecting anticipated median values.

Following randomization, subjects will be given a supply of study drug with instructions to take the study drug twice daily using a 2-week dose escalation schedule. Subjects will titrate to two 25mg tablets twice daily, or the maximally tolerated dose.

5. STUDY INTERVENTIONS/ STUDY DRUG

5.1. Study Drug and Dose Selection

The intervention under study is oral topiramate, 100mg daily taken in two divided doses of 50mg. Matching placebo will be identical to topiramate in color, shape, and packaging.

5.2. Dose selection

Previous studies have evaluated topiramate as a potential therapy for pain associated with diabetic neuropathy with mixed results. The dose in these trials varied from 100-400 mg daily[22,23,64]. The objective of this study is to evaluate the potential efficacy of topiramate as a disease modifying therapy for CSPN associated with metabolic syndrome. Randomized trials in diabetic neuropathy have demonstrated that a dose of 100 mg/day is sufficient to improve both neuropathy associated QOL (as measured by NQOL-DN) and thigh IENFD [24,25], while side effects of decreased concentration or fatigue were more common at higher doses. Similarly, a Cochrane review reported no additional benefit to doses over 100 mg daily in topiramate trials for headache[65]. In light of the greater risk of side effects at doses over 100 mg daily, these data support selection of the 100 mg/day target dose.

5.3. Formulation and Packaging

Study drug, or matching placebo, will be provided in labeled packages with sufficient product for study subjects to take four capsules daily for 16 weeks, with sufficient overage in each package to allow for anticipated variation in visit scheduling. Four 132-count bottles will be provided, permitting for 14 days of overage. Each study test article packet will be labeled with the following information:

Name of Sponsor
Name and address of study drug distribution center
Study number and IND number
Unique drug package number
Drug treatment label (each kit will list either 25 mg topiramate or placebo)
Route of administration
Quantity of dose unit
Directions for use
Storage conditions
Space for investigator name, telephone, dispensing date and subject number
Space for study subject identifier
Label statement “Caution: New Drug-Limited by federal law to investigational use”

Label statement “Caution: Keep out of reach of children”

5.3.1. Supplies and Dispensation

Study drug supplies will be received by the site investigator or other authorized study personnel at the study site, managed and stored safely and properly, and kept in a secured location with restricted access. Study staff with responsibility for drug management will keep accurate and complete records of study drug received by the site, dispensed to study subject, and used and returned by study subject.

Study drug will be dispensed by appropriately qualified staff as designated by the investigator’s delegation of authority log. Subjects will self-administer the study drug at home following the instructions provided to the subject at the study visit. The study site investigator will retain returned study drug, or study drug supplies not dispensed to subjects, until the sponsor provides written instructions for disposition.

The study case report forms and source documents will include prompts to record study subject eligibility to receive study drug, study drug dispensed, dosing start date, dosing end date, missing doses, and study drug returned.

5.3.2. Titration Schedule and Dose Adjustments

Subjects randomized to the topiramate arm will start 25mg topiramate once daily in the evening. On day 4 following randomization a morning dose of 25 mg will be added. On day 8 following randomization an addition 25 mg tablet will be added in the evening, and on day 12 a second morning dose will be added so that the subject will be taking a total of 50mg twice daily. Subjects who experience an adverse event during the dose titration may continue at the highest tolerated dose for one week prior to an additional attempt to increase to the targeted dose. Those who are tolerant of a lower dose but intolerant of the target dose will continue on the highest tolerated dose. Results will be analyzed in an intent to treat fashion. If a subject develops a treatment related adverse event, the dose may be lowered at the discretion of the site PI in order to establish a lower maximally tolerated dose. Those who have an adverse event and are unable to continue medication will undergo a termination visit.

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount received from the central pharmacy, and the amount destroyed upon completion of the study. An investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. The inventory will include details of *topiramate* received and dispensed to subjects, batch, and ID numbers. All unused *capsules* must be kept until reconciliation of delivery records with accountability logs by the monitor. After the monitor has performed accountability, the site will be instructed by the DCC or designee to either destroy the remaining study drug or return it to the

Central Pharmacy or manufacturer. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of topiramate received and dispensed drug must be reconciled.

5.4. Concomitant Interventions

The following are permissible as concomitant interventions for neuropathic pain related to CSPN if stable for 8 weeks prior to screening:

- Gabapentin
- Pregabalin
- Tricyclic antidepressants
- Duloxetine
- Venlafaxine
- Tramadol (200mg daily or less)
- Topical lidocaine
- Non-steroidal anti-inflammatory drugs

The intent of the protocol is to keep allowable neuropathic pain agents and dosing unchanged for the duration of the study (8 weeks prior to screening through week 96).

Marijuana, cannabinoids, and alpha lipoic acid (ALA) will be specified as neuropathic pain agents on the concomitant medication form. These products will not require dosing stability, but will be tracked to evaluate any potential impact on outcomes.

If in the opinion of the site investigator, changes in the permissible neuropathic pain agents are required for the safety and/or well-being of the participant between baseline and week 96/ET, the change will be captured in EDC and reported to the PPI. These participants will not be required to discontinue study medication or exit the study.

5.4.1. Prohibited Medications/Interventions

The following medications/interventions are exclusionary:

- Therapeutic anticoagulations including coumadin or oral factor X or thrombin inhibitor therapy
- Topical capsaicin
- Oral prednisone
- Carbonic anhydrase inhibitor (such as acetazolamide)
- Weight loss medications
- Neuropathic pain agents beyond first line agents
- Scheduled opiates, or as needed opiate medications more than three times weekly
- Intrathecal pain pump or spinal cord stimulator
- Current or prior history of topiramate therapy

5.5. Subject Compliance

At each study visit, the site Investigator and/or Study Coordinator will assess the subject's compliance with the study requirements. This will include checks for protocol compliance, including use of study drug in order to assess the reliability of subject-generated data. Subjects who fail to comply with study requirements may be withdrawn from the study.

A serum topiramate level will be measured at baseline and weeks 32, 64, and 96 or ET to assess for compliance or potential crossover (e.g. a participant randomized to placebo taking off study prescription topiramate).

Participants will be asked to hold their morning dose of study medication until after the blood draw at weeks 32, 64, 96/ET. The date and time of last dose of study drug will be recorded. If the participant does not hold the prior dose, the topiramate level should still be obtained. These data will not be shared with the study team until after the study has closed.

6. STUDY PROCEDURES

6.1. Schedule of Assessments

Recruitment will take place over 48 weeks. The study will consist of screening and baseline visits, safety and monitoring visits every 16 weeks, evaluation visits at 32, 64, and 96 weeks, and a final safety assessment visit or telephone assessment following termination of study drug. A Schedule of Assessments is provided in Appendix A.

6.2. Visit 01 Screening (Day -30 to 0)

Up to 30 days will be allotted to complete the screening assessments. Prior to any involvement in study related activities, the participant must sign and date a central Institutional Review Board (IRB) approved written informed consent form (ICF). A copy of the signed and dated ICF must be given to the participant. Screening visit procedures may be performed over two consecutive days if scheduling constraints prohibit the completion of all study procedures in a single day. If screening procedures are completed over two days, the baseline visit will occur within 30 days of the last screening procedure completion.

The following procedures will be performed at the screening visit (this visit may take approximately 3 hours):

- Obtain written informed consent from participant.
- Review inclusion/exclusion criteria.
- Obtain a medical, family, and neurological history to assess for possible exclusionary conditions. Medical histories should include baseline symptoms, ongoing illnesses, other chronic conditions, surgical history, review of currently used medications, as well as any other important information that may affect the conduct of the study. See section 7.1.3.

- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.19.
- Perform a general medical and detailed neuromuscular physical examination. See section 7.1.5.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg), height (cm) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform a resting 12-Lead ECG. See section 7.1.8.
- Collect blood samples for CBC, fasting basic metabolic panel, fasting insulin, fasting lipid panel, two-hour OGTT, HgbA1C, Vitamin B12, and serum immunofixation and serum pregnancy test (pregnancy test for women of child-bearing potential only). See section 7.1.12.
- Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.
- Perform clinical assessment for suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.

All clinical and laboratory evaluations, procedures related to inclusion/exclusion criteria, or assessments performed during treatment will be reviewed, initialed and dated by the Principal Investigator or the individual specifically designated by the investigator on the delegation of responsibility (DOR) log.

6.3. Re-screening

In the event a participant is originally found to be ineligible at the screening visit, but the investigator believes they may subsequently be eligible based on changes to the participant's circumstances or the study protocol, the participant may return for another screening visit (re-screening visit). If the original screening visit was conducted greater than 90 days before the re-screening visit, the re-screening visit will be treated the same as the original screening visit (see section 6.2).

- If the original screening visit was conducted **within 90 days** prior to the re-screening visit, the following data may be re-used from the original screening visit:
    - Serum immunofixation
    - Two-hour OGTT
    - Vitamin B12 results
    - Resting 12-Lead ECG
- If the original screening visit was conducted **within 30 days** prior to the re-screening visit, the following may be re-used from the original screening visit:
    - General medical and detailed neuromuscular physical examination results.
    - Vital sign measurements including blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C).

- Weight (kg) and height (cm) measurements, and the calculated Body Mass Index (BMI).
- Waist circumference (cm) measurement.
- Blood sample results for CBC, fasting basic metabolic panel, fasting insulin, fasting lipid panel, two-hour OGTT, HgbA1C, Vitamin B12, and serum immunofixation and serum pregnancy test (pregnancy test for women of child-bearing potential only).
- *Utah Early Neuropathy Scale* (UENS) results.
- *Columbia-Suicide Severity Rating Scale* (C-SSRS) results.

- The following procedures **must be repeated** regardless of timeframe between the original screening visit and re-screening visit:
  - Review inclusion/exclusion criteria.
  - Detailed medical, family, and neurological history to assess for possible exclusionary conditions.
  - Review concomitant medications, including all nutritional, herbal and alternative therapies.
  - Informed Consent
- If a participant being rescreened had NCS performed as part of a prior screening visit, these data may be used for baseline data (assuming the participant proceeds to randomization) if the baseline visit occurs within 90 days of the original NCS performance date.

All clinical and laboratory evaluations, procedures related to inclusion/exclusion criteria, or assessments performed during treatment will be reviewed, initialed and dated by the Principal Investigator or the individual specifically designated by the investigator on the delegation of responsibility (DOR) log.

6.4. Visit 02 Baseline (Day 0)

Participants who continue to meet all inclusion/exclusion criteria after screening will present to the clinic for the baseline visit. The baseline visit will be performed within 30 days of the screening visit. However, the investigator will review, date and initial the screening laboratory assessments to confirm participant eligibility for study participation prior to the baseline visit procedures. Therefore, adequate time must be provided for the laboratory results to be received from the central laboratory. The investigator or designee will again review the study inclusion/exclusion criteria and participant medical history, confirming that the participant meets criteria for study participation before randomization.

The following procedures will be performed at the baseline visit (this visit may take about 4 hours):

- Review Inclusion/Exclusion criteria.
- Obtain a medical, family, and neurological history to assess for possible exclusionary conditions. Medical histories should include baseline symptoms, ongoing illnesses, other chronic conditions, surgical history, review of currently used medications, as well as any other important information that may affect the conduct of the study. See section 7.1.3.

- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Review interval medical history.
- Review adverse events.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Perform an abbreviated Physical Examination, including visual field and fall risk assessment.
- Perform Functional and Mobility testing (6MWT, TUG, ABC Scale). See section 7.1.11.
- Perform nerve conduction studies. See section 7.1.13.
- Perform distal thigh skin biopsy. See section 7.1.14.
- Collect blood samples for routine hematology panel blood, basic metabolic panel, topiramate level and DNA analysis (OPTIONAL). See section 7.1.12.
- Collect urine for a urine pregnancy test (pregnancy test for women of child-bearing potential only).
- For women of childbearing potential and sexually active males, review acceptable birth control methods that must be used during the study.
- Perform subject randomization via interactive voice response system (IVRS) and/or interactive web response system (IWRS). See section 4.4.5.
- Dispense study drug.
- Instruct subject about correct administration and titration of study drug. See section 5.3.2.
- Instruct subject to bring unused study drug to each study visit, and to immediately report any AEs to the Investigator or Coordinator.
- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
- Perform clinical assessment for suicide ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.
- Complete the Rapid Assessment of Physical Activity (RAPA) Survey. See section 7.1.17.

6.5. Visit 03 Week 16 (± 7 days)

This safety follow-up visit will occur within ± 7 days of the targeted visit date. The following procedures will be performed at the Week 16 visit (this visit may take about 3 hours):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform an Abbreviated Physical Examination including visual field examination and assessment for fall risk.

- Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.
- Collect blood samples for safety monitoring laboratory assessments including basic metabolic panel, CBC and serum pregnancy test (pregnancy test for women of child-bearing potential only). (Refer to University of Rochester Medical Center Lab Manual for sample handling and processing requirements). See section 7.1.12.
- Dispense study drug.
- Perform study drug reconciliation and container collection.
- Assess study drug compliance.
- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
- Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.19.
- Perform clinical assessment for suicide ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.

6.6. Visit 04 Week 32 (± 7 days)

The follow-up visit will take place within ± 7 days of the targeted visit date. The following procedures will be performed at the Week 32 evaluation visit (this visit may take about 4 hours):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform an abbreviated Physical Examination, including visual field and fall risk assessment.
- Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.
- Perform Nerve Conduction Studies (NCS). See section 7.1.13.
- Perform distal thigh skin biopsy. See section 7.1.14.
- Collect blood samples for OGTT, CBC, fasting basic metabolic panel, fasting insulin, fasting lipid panel, HgbA1C, topiramate level and serum pregnancy test for women of child-bearing potential only. See section 7.1.12.
- Perform Functional and Mobility testing (6MWT, TUG, ABC Scale). See section 7.1.11.
- Dispense study drug.
- Perform study drug reconciliation and container collection.
- Assess study drug compliance.

- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
  Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.19.
- Perform clinical assessment for suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.
- Complete the Rapid Assessment of Physical Activity (RAPA) Survey. See section 7.1.17.

6.7. Visit 05 Week 48 (± 7 days)

This safety follow-up visit will occur within ± 7 days of the targeted visit date. The following procedures will be performed at the Week 48 evaluation visit (this visit may take about 3 hours):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform an abbreviated Physical Examination, including visual field and fall risk assessment.
- Collect blood samples for safety monitoring laboratory assessments including basic metabolic panel, CBC and serum pregnancy test (pregnancy test for women of child-bearing potential only). See section 7.1.12.
- Dispense study drug.
- Perform study drug reconciliation and container collection.
- Assess study drug compliance.
- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
- Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.
- Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.19.
- Perform clinical assessment for suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.

6.8. Visit 06 Week 64 (± 7 days)

The follow-up visit will take place within ± 7 days of the targeted visit date. The following procedures will be performed at the Week 64 evaluation visit (this visit may take about 4 hours):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform an abbreviated Physical Examination, including visual field and fall risk assessment.
- Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.
- Perform Functional and Mobility testing (6MWT, TUG, ABC Scale). See section 7.1.11.
- Perform Nerve Conduction Studies (NCS). See section 7.1.13.
- Perform distal thigh skin biopsy. See section 7.1.14.
- Collect blood samples for OGTT, CBC, basic metabolic panel, fasting insulin, fasting lipid panel, HgbA1C, topiramate level and serum pregnancy test for women of child-bearing potential only. See section 7.1.12.
- Dispense study drug.
- Perform study drug reconciliation and container collection.
- Assess study drug compliance.
- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
- Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.19.
- Perform clinical assessment for suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.
- Complete the Rapid Assessment of Physical Activity (RAPA) Survey. See section 7.1.17.

6.9. Visit 07 Week 80 (± 7 days)

This safety follow-up visit will occur within ± 7 days of the targeted visit date. The following procedures will be performed at the Week 80 visit (this visit may take about 3 hours):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform an abbreviated Physical Examination, including visual field and fall risk assessment.
  Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.

- Collect blood samples for safety monitoring laboratory assessments including basic metabolic panel, CBC, and serum pregnancy test (pregnancy test for women of child-bearing potential only). See section 7.1.12.
- Dispense study drug.
- Perform study drug reconciliation and container collection.
- Assess study drug compliance.
- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
- Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.19.
- Perform clinical assessment of suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.

6.10. Visit 08 Week 96 Termination (± 7 days)

The final study treatment visit will occur 96 weeks following baseline. All assessments performed at the evaluation visits will take place. The investigator will perform a complete physical examination. All study drug and study drug packages will be collected from the subject at this visit and a final assessment of study drug compliance will be calculated. The Week 96 visit will occur within ± 7 days of the targeted visit date.

The following procedures will be performed at the Week 96 visit (this visit may take about 5 hours):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform a general medical and detailed neuromuscular physical examination. See section 7.1.5.
- Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.
- Perform Functional and Mobility testing (6MWT, TUG, ABC Scale). See section 7.1.11.
- Perform Nerve Conduction Studies (NCS). See section 7.1.13.
- Perform distal thigh skin biopsy. See section 7.1.14.
- Collect blood samples for fasting basic metabolic panel, CBC, fasting insulin, fasting lipid panel, two-hour OGTT, topiramate level and HgbA1C. See section 7.1.12.
- Perform study drug reconciliation and container collection.
- Assess study drug compliance.
- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
- Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.19.

- Perform clinical assessment for suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.
- Complete the Rapid Assessment of Physical Activity (RAPA) Survey. See section 7.1.17.

6.11. Visit 09 Safety Assessment

A safety call or visit will occur 4 weeks (+/- 7 days) following the last dose of study drug. The following procedures will be performed at the safety assessment (this visit may take up to 2 hours).

If the Site PI determines a Safety Call is appropriate for final safety assessment, the following information should be collected;

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.

If the Site PI determines a Safety Visit is required for either a final safety assessment or an unscheduled safety visit the following additional procedures can be performed (optional safety data based on clinical judgement of site PI):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Perform a general medical and detailed neuromuscular physical examination. See section 7.1.5.
- Collect blood samples for basic metabolic panel and CBC. See section 7.1.14.
- Perform clinical assessment for suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.

6.12. Early Termination Visit (≤ 30 ± 7 days)

The following procedures will be performed at the early termination visit (this visit may take about 5 hours):

- Review interval medical history.
- Review adverse events.
- Review concomitant medications, including all nutritional, herbal and alternative therapies. See section 7.1.4.
- Perform vital sign measurements: blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C). See section 7.1.6.
- Record weight (kg) and Body Mass Index (BMI).
- Record waist circumference (cm). See section 7.1.7.
- Perform a general medical and detailed neuromuscular physical examination. See section 7.1.5.
- Perform Functional and Mobility testing (6MWT, TUG, ABC Scale). See section 7.1.11.

- Perform Nerve Conduction Studies (NCS). See section 7.1.13.
- Perform distal thigh skin biopsy. See section 7.1.14.
- Collect blood samples for fasting basin metabolic panel, CBC, fasting insulin, fasting lipid panel, topiramate level, two-hour OGTT and HgbA1C. See section 7.1.12.
- Perform study drug reconciliation.
- Administer the *Neuropathy Total Symptom Score-6* (NTSS-6) to the subject. See section 7.1.9.
- Administer the *Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)* BPI-DN. See section 7.1.9.
- Administer the *Utah Early Neuropathy Scale* (UENS). See section 7.1.10.
- Administer the *Norfolk Quality of Life-Diabetic Neuropathy scale* (NQOL-DN). See section 7.1.16.
- Perform clinical assessment for suicidal ideation with the *Columbia-Suicide Severity Rating Scale* (C-SSRS). See section 7.1.15.
- Complete the Rapid Assessment of Physical Activity (RAPA) Survey. See section 7.1.17.

6.13. Early Termination and Premature Withdrawal

Subjects have the right to withdraw from the study at any time without prejudice. The site Investigator may withdraw study drug from a subject in the study in the event of intercurrent illness, adverse events, other reasons concerning the health or well-being of the subject or other administrative reasons. Early termination will be implemented in the case of emergency disclosure of drug treatment (i.e., unblinding). **NOTE: All efforts should be made by study staff to encourage subjects to return for follow-up visit(s). If a subject withdraws consent from the study in writing, no further contact can be made.**

A subject may discontinue study medication for the following reasons:

Administrative

1. Withdrawal of consent
2. Request of Sponsor or Principal Investigator
3. Request of primary care physician
4. Pregnancy
5. Subject deemed lost to follow up/failure to return
6. Termination of study
7. Other

Adverse Event

1. Worsening of the disease under study
2. Worsening of pre-existing disease (other than disease under study)
3. Intercurrent illness
4. Death
5. Major/clinically significant alteration in laboratory values after beginning study drug
6. Suicidality based on the C-SSRS
7. Other adverse event

In the event a participant discontinues study medication for any reason, every effort should be made to complete the evaluation visits at week 32, 64, and 96. An early termination visit should be completed for all participants who are unable or unwilling to complete additional evaluation visits. If a subject is unable to return to the site, or refuses to complete all termination visit procedures, any reasonable study procedures to which the subject consents will be completed.

Should a scheduled in-person visit be impossible, conduct as many of the verbal assessments as possible, with special emphasis on obtaining information on possible AEs, and arrange for return of study drug. Every effort will be made to determine the subject's health status at withdrawal.

Reasons for early termination of the subject prior to completion of the study must be stated in the CRF and in the site source documentation for all study subjects who were enrolled in the study. The CCC and the IMM must be informed within 24 hours of all study subjects who are withdrawn due to an adverse event.

6.13.1. Premature Drug Discontinuation

Subjects who prematurely discontinue study drug will be questioned regarding reasons for discontinuation. Subjects will be encouraged to restart study drug following the guidelines in section 6.12.2.

6.13.2. Restarting Study Drug after Premature Drug Discontinuation

Subjects who discontinue study drug for less than one week will be asked to restart at the prior dose. Those who failed to take study drug for 1-7 days will be asked to restart at the previous dose. Those not having taken study drug for 8-14 days will restart at half of the prior dose. Those not having taken study drug for 15 days or more will restart the titration. Those who discontinued due to an adverse event will restart at a dose lower than the maximally tolerated dose and titrate to that dose.

6.13.3. Missed Doses

Subjects who miss a dose will continue the planned dosing schedule and will not supplement the next dose with that which was missed.

6.13.4. On Study/Off-Intervention Evaluations

Every possible effort should be made by the site PI to encourage subjects who are no longer taking study drug to remain in the study. They should explain that continued participation will teach us more about the natural history of CSPN progression, the impact of metabolic improvement and weight loss on CSPN, and the clinical relevance of IENFD and other surrogate measures of CSPN progression.

When subjects decide to go off the study drug, it will be a reportable event and the project manager will discuss the reasons for this with site staff to learn the specifics in each case and provide advice on an individual basis about the best ways to keep the subject engaged in the

project. These subjects and their physicians will not be told whether they were given topiramate or placebo.

6.14. Off-Study Requirements

Adverse events will be followed up to 30 days after study completion (including early termination) or until the site Principal Investigator deems the condition to have resolved or the condition has stabilized (whichever occurs first).

6.15. Pregnancy

Women who become pregnant while in the study will have the study drug withdrawn immediately, will be asked to return for a final in-person evaluation, and will be followed according to adverse event reporting procedures until birth or conclusion. Generally, follow-up will not exceed 8 weeks following the estimated delivery date.

6.16. Diabetes

Patients who meet ADA criteria for diabetes at screening will be excluded. Those who develop diabetes during the course of the study may continue in the study. However, in the event a participant is found to have diabetes on follow up metabolic testing, their primary care provider will be notified.

7. SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

7.1.1. Informed Consent

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are performed and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, approved by the NeuroNEXT CIRB, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study.

7.1.2. Protocol Violations

The site monitor is responsible for collection of all protocol deviations that occur during the course of the study to ensure proper reporting in the clinical study report.

Generally, any activity that is not performed as outlined in the protocol should be categorized as a 'Protocol Deviation'. Missed visits and any procedures not performed (not attempted) for reasons other than illness, injury or progressive disability (i.e., subject is physically unable to

perform test) will be reported as protocol deviations. Procedures or visits not performed due to illness, injury or disability, including procedures that were attempted but failed (i.e., blood samples unable to be drawn after multiple attempts, or weight unable to be obtained due to subject immobility) will not be reported as protocol deviations. Deviations fall into two categories, 'major' and 'minor', and are defined as follows:

Major: Any deviation that impacts safety, welfare, or rights of a study subject, or impacts the primary outcome of the study (safety assessments). Examples include: Informed Consent issues affecting a subject's rights, Inclusion/Exclusion violations, Missed Assessments affecting safety endpoints, Study Drug Administration that affects a study endpoint or the subject's welfare. A major deviation is also termed a protocol violation.

Minor: Any deviation that does not fall within the above category. Examples include: out of window or missed study assessments that do not affect study endpoints or the subject's welfare.

7.1.3. Medical History

A complete medical history including lifestyle questions (i.e., tobacco and alcohol use) will be obtained at screening and prior to randomization.

7.1.4. Concomitant Medications/Treatments

All concomitant medications must be recorded, including, but not limited to all vitamins, supplements, nutritional, herbal and alternative therapies.

7.1.5. Physical Examination

A general medical and detailed neuromuscular physical examination will be performed in order to exclude medical conditions precluding participation, and to confirm symptoms consistent with distal symmetric polyneuropathy. The neurological examination will include a baseline assessment of visual fields.

7.1.6. Vital Signs

Vital signs will be obtained after the subject has been sitting for five minutes. Vital signs include blood pressure (systolic and diastolic), heart rate (beats/minute), and body temperature (°C).

7.1.7. Waist Circumference

Waist circumference will be measured in centimeters (cm) while standing. Measurement will be performed at the level of the iliac crest after expiration.

7.1.8. Electrocardiogram (ECG)

An electrocardiogram (ECG) will be performed to exclude a baseline prolonged QTc interval. ECGs with QTc interval more than 430 ms in men, or 450 ms in women will be reviewed at each

site. Participants with QTc more than 450 ms in men, or 470 ms in women will be considered screen failures. Electrocardiogram's are not required to be reviewed by the site cardiologist.

7.1.9. Neuropathy Symptom Assessment

Neuropathy Total Symptom Score -6 (NTSS-6) [53] is a brief inventory of neuropathy symptoms that has demonstrated reliability and validity in diabetic neuropathy.

Brief Pain Inventory – Diabetic Neuropathy (BPI-DN) [54,55] is a validated pain inventory that assesses pain severity related to CSPN.

7.1.10. Utah Early Neuropathy Scale (UENS)

Utah Early Neuropathy Scale (UENS) [48] will be performed by the investigator to confirm diagnosis and exclude patients with severe neuropathy.

7.1.11. Functional and Mobility Testing

Functional and mobility testing, fitness and proactive balance will be assessed because balance and fall risk are major clinically relevant outcomes for patients with CSPN.

- *A 6-minute walk test (6MWT)* will be performed on a standard course that will be used throughout the study. The 6MWT has demonstrated reproducibility in obese participants[56] and has been shown to correlate with intermuscular adipose tissue, a depot of adipocytes related to insulin resistance and increased in patients with metabolic syndrome[57].
- *A Timed up and Go (TUG)* will be performed as a measure of proactive balance and fitness. TUG times are normally distributed, resistant to ceiling effects[58] and are reduced in patients with neuropathy in the setting of diabetes relative to control participants[59]. Among commonly employed fall risk assessments, the TUG had the highest diagnostic accuracy[60].
- The Activities-specific Balance Confidence (ABC) Scale. The ABC scale is a self-administered instrument assessing balance and gait confidence.[89]

7.1.12. Laboratory Evaluations

Clinical laboratory evaluations for the study will be analyzed by the NeuroNEXT central laboratory at the University of Rochester. Refer to the *University of Rochester Medical Center Lab Manual* for sample handling and processing requirements.

The following laboratory assessments will be performed throughout the study:

- Safety monitoring laboratory tests:
  - Complete Blood Count (CBC)
  - Basic Metabolic Panel (BMP) including Sodium, Potassium, Chloride, Carbon Dioxide, Urea Nitrogen, Glucose, Creatinine, Calcium, and Anion Gap (optional).
  - Hematology Panel
  - Serum Pregnancy Test (for women of child-bearing potential only)
  - Urine Pregnancy Test (for women of child-bearing potential only)

- Baseline metabolic monitoring laboratory tests. These are intended to assess the metabolic effects of therapy and to confirm the presence of metabolic syndrome for inclusion criteria and evaluation throughout the study:
    - Fasting Insulin
    - Fasting Lipid Panel including Cholesterol, Triglycerides, Calculated LDL Cholesterol, and HDL Cholesterol.
    - 2-hour Oral Glucose Tolerance Test (OGTT) using a 75g anhydrous dextrose oral load with the first blood draw (pre-dextrose) prior to 10 am. The second draw will be 2 hours post dextrose. The subject will remain sedentary during the following two hours.
    - HgbA1C
- Laboratory evaluation for additional causes for neuropathy:
    - Vitamin B12
    - Serum Immunofixation
- Serum topiramate levels will be measured at Baseline and weeks 32, 64, and 96 (or ET) in order to assess for compliance and treatment crossover.

  Participants will be asked to hold their morning dose of study medication until after the blood draw at weeks 32, 64, 96/ET. The date and time of last dose of study drug will be recorded. If the participant does not hold the prior dose, the topiramate level should still be obtained.

  Topiramate laboratory kits, shipping materials, and requisitions will be provided by Utah. The sample will be obtained in a red collection tube with serum separated by centrifuge within 2 hours. Serum will be placed in the transport vial and refrigerated prior to being placed on a cold pack for shipment. The sample will be returned to Utah with the skin biopsy sample. Samples should be received by Utah cool (not frozen). The results will be made available to the DSMB.
- DNA sample (OPTIONAL)
  DNA samples can be collected at Baseline using supplies provided by URMC. Centrifuge the EDTA tube at 1500 RPM for 15 minutes. The buffy coat will be transferred into cryovials and stored at -80C. At the end of the enrollment period, sites will batch ship all the buffy coat samples to Utah with shipment kit and air bills provided.

All clinical and laboratory evaluations, procedures related to inclusion/exclusion criteria, or assessments performed during treatment will be reviewed, initialed and dated by the Principal Investigator or the individual(s) specifically designated by the investigator on the DOR log. The Investigator must indicate if out of range lab values are Clinically Significant (CS) or Not Clinically Significant (NCS) on the lab report.

7.1.13. Nerve Conduction Studies

Nerve conduction studies (NCS) will be performed at baseline and each evaluation visit. NCS will be performed on the left leg unless focal skin or orthopedic lesions preclude safe or accurate performance of NCS in this limb, in which case NCS will be performed on the right leg. NCS of the Sural sensory and Peroneal motor nerves with distal latency/conduction velocity, Peroneal motor conduction velocity in the leg segment (between the ankle and knee).

Definition of CSPN: For the purposes of CSPN diagnosis, an absent or low amplitude sural sensory response is required (as defined below).

Detailed protocol: NCS will be performed using standard techniques. Unless there is a local process such as a skin lesion, prior traumatic injury, history of radiculopathy etc. Skin temperature must be maintained > 31°C. Temperature should be recorded from the dorsal foot and documented. T

The sural sensory response will be performed in an antidromic fashion with stimulation 14 cm proximal to the recording electrode, which will be placed posterior to the lateral malleolus. Subsequently, two additional responses will be recorded using a sweep speed of 2 msec/division and an appropriate sensitivity setting. Three responses will be averaged using the same sweep and gain settings, from which amplitude and distal latency will be derived.

The peroneal motor response will be recorded from the EDB muscle with stimulation 9 cm proximally at the ankle, and at the level of the fibular head. Obtain a single waveform at each simulation site, marking the onset latencies and baseline to peak amplitudes. The conduction velocity will be calculated. The minimal F wave latency will be measured using a sensitivity of 200-500 uV/division and at least 10 stimuli.

The waveforms will be uploaded to the central NCS laboratory at the University of Utah for immediate review. This review will ensure adequate adherence to protocol (temperature, stimulation location, averaging) and technical quality (baseline stability, absence of artifact). If after review, technical deficiencies are noted, the site will be notified and the selected NCS will be repeated[51].

7.1.14. Skin Biopsy

The left leg is the preferred site for skin biopsy. The left lower extremity will be evaluated by study staff to rule out previous surgery at the hip or proximal to the knee. The site of biopsy should not have scarring, rash, burns, significant edema, or tattoos. If any of these conditions are present, the right leg should be similarly evaluated, and biopsied, if appropriate. All biopsies should be performed from the same side throughout the study, unless reasonable justification is documented (ie: trauma or surgery to previously used side).

A 3mm punch biopsy will be taken from the selected the biopsy site using local anesthesia (lidocaine with epinephrine) using standardized techniques. The punch will be placed in fixative and shipped overnight courier to the Utah Cutaneous Nerve Laboratory, where the tissue will be processed and stained using PGP9.5 and intraepidermal nerve fiber density (IENFD) measured[62.]

Details of the skin biopsy procedure, sample handling, processing and shipping are available in the reference manual for skin biopsy.

7.1.14.1. Distal Thigh Skin Biopsy

A distal thigh skin biopsy is collected at the following visits: Baseline (Visit 02), Week 32 (Visit 04), Week 64 (Visit 06), and Week 96 (Visit 08/Termination) and/or Early Termination.
A 3mm punch biopsy will be taken from the distal, lateral thigh 10 cm distal to superior margin of the patella.

Refer to the *Reference Manual for skin punch biopsy*.

7.1.15. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation rating scale. It measures a Subject's degree of suicidal ideation on a scale ranging from wishing to be dead without an active plan to active suicidal ideation with a specific plan and intent to die. Only investigators who have been fully trained in the administration of the C-SSRS will assess subject suicidality. As part of training, investigators are prepared to respond to and manage instances in which patients express suicidal ideation or exhibit suicidal behavior.

7.1.16. The Norfolk Quality of Life – Diabetic Neuropathy (NQOL-DN) Scale

Patient reported neuropathy related QOL. The NQOL-DN is a validated neuropathy specific QOL measure. Factor analysis has been used to group NQOL-DN items into 6 subscores: symptoms, autonomic, small fiber, large fiber, and activities of daily living[27].

7.1.17. The Rapid Assessment of Physical Activity (RAPA) Survey

The RAPA is a validated patient reported survey that quantifies the intensity and frequency of aerobic and strength activity.[90] The RAPA is included in order to assess the degree of exercise

and physical activity between the treatment groups. This is important because intensive exercise programs may impact the natural history of CSPN associated with prediabetes.

7.1.18. Subject Adherence Assessments

At each study visit, the site Investigator and/or Study Coordinator will assess the subject's compliance with the study requirements by performing study drug reconciliation and collecting study drug containers. This will also include reviewing protocol compliance, including use of study drug and concomitant medications. If applicable, subjects who fail to comply with the study requirements may be removed from the study.

The site Investigator and/or Study Coordinator will conduct monthly telephone calls between clinic visits (i.e.: between Baseline and Week 16 calls should occur at Week 4, Week 8, and Week 12) to encourage protocol compliance and enhance retention.

7.1.19 Optional Tissue Banking

DNA samples will be collected at Baseline using supplies provided by URMC. Centrifuge the EDTA tube at 1500 RPM for 15 minutes. The buffy coat will be transferred into cryovials provided by Utah and stored at -80C. At the end of the enrollment period, sites will batch ship all the buffy coat samples to Utah with shipment kit and air bills provided.

Skin biopsy tissue collected for IENFD testing for will be stored at the Utah Cutaneous Nerve Lab until study closure. Samples from participants who consent to long-term tissue storage will be placed in long-term tissue banking and the rest will be destroyed.

The DNA and tissue bank will be located in the laboratory of Rob Singleton, MD, at the University of Utah. Participants can withdraw consent to bank their samples by notifying their CSS investigator. Banking preferences will be entered into the EDC by the CSS staff. At the end of the study, DNA or tissue in the bank will be destroyed if participants opt out of banking at any time during the study or do not mark and initial their preference on the consent form.

8. MANAGEMENT OF ADVERSE EVENTS

Extensive data regarding safety and adverse events are available from clinical trials of topiramate for epilepsy and episodic migraine. The dose of topiramate to be used in the TopCSPN Study is similar to that used for episodic migraine (50-200mg daily). Adverse events observed in randomized trials for migraine will be summarized[65]. Following this summary, potentially significant adverse events observed at higher doses will be listed.

When topiramate must be discontinued for participant safety, the dose can be stopped immediately or titrated down based on the clinical judgement of the site investigator.

Adverse Events Observed at 100 mg daily of topiramate:

- Anorexia. Loss of appetite is one of the mechanisms contributing to weight loss. Most commonly anorexia is mild. In subjects complaining of intolerable anorexia, the dose will be tapered to the maximal tolerated dose.
- Fatigue. Subjects complaining of intolerable fatigue will be asked to taper the dose to the maximum tolerated.
- Memory Problems. Topirmate may cause confusion, psychomotor slowing, poor concentration, or memory loss. These symptoms are more commonly observed with rapid dose escalation. Patients complaining of intolerable memory problems, or those observed to have cognitive dysfunction sufficiently significant to warrant dose modification in the opinion of the PI will taper their dose to that maximally tolerated.
- Nausea. Subjects complaining of intolerable nausea will be asked to taper the dose to the maximum tolerated.
- Paresthesias. Paresthesias are typically mild and uncommonly lead to discontinuation. In the setting of this study, paresthesias may also be related to the underlying disease (CSPN), or nerve regeneration. There are no data suggesting topiramate causes or worsens peripheral neuropathy. Subjects experiencing increased paresthesias will be encouraged to continue to participate unless the symptom is severe enough in the opinion of the PI to warrant dose reduction.

Potentially serious adverse events noted in the package insert include:

- Glaucoma. Topiramate has been reported to cause acute myopia associated with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating therapy, and include decreased visual acuity and ocular pain. Ophthalmologic findings can include myopia and ocular hyperemia (redness). Mydriasis may or may not be present. Visual acuity will be assessed at each visit and subjects with reduced acuity, ocular pain, or ocular hyperemia will discontinue medication and be immediately referred for ophthalmologic examination.
- Kidney stones. 1.5% of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2 to 4 times greater than expected in a similar, untreated population. Carbonic anhydrase inhibitors (Topiramate, but also zonisamide, acetazolamide or dichlorphenamide) can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH.
- Metabolic acidosis. Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Renal disease, severe respiratory disorders, status epilepticus, diarrhea, and ketogenic diet may increase this risk. Symptoms may include hyperventilation, fatigue, anorexia, or rarely cardiac arrhythmias or stupor. Serum electrolytes including bicarbonate will be measured at each study visit. Subjects with a total bicarbonate of < 17 mEq/L and a > 5 mEq/L decrease from pretreatment will discontinue treatment.
- Oligohidrosis (decreased sweating) and subsequent loss of temperature regulation with hyperthermia has been reported in adults, especially in combination with carbonic anhydrase inhibitors and anticholinergic medications. Subjects complaining of significant reduction in sweating will taper medication to the maximum tolerated dose.
- Visual field defects (independent of elevated intraocular pressure) have been reported in clinical trials and in postmarketing experience. Visual fields will be assessed at each study

visit. Patients observed to have new visual field abnormalities will be referred for ophthalmologic examination and medication will be discontinued.

8.1. Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies that occur during paternal or maternal exposure to study drug (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the subject has been withdrawn from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the Coordination Center.

9. PROTOCOL AMENDMENTS AND STUDY TERMINATION

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the CIRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the CIRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

The Sponsor and NeuroNEXT Network reserve the right to discontinue the study at a clinical study site(s) for safety or administrative reasons at any time. Should the study be terminated and/or the clinical study site closed for any reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative.

10. STATISTICAL CONSIDERATIONS

The NeuroNEXT Data Coordinating Center has developed a statistical analysis plan, in collaboration with the protocol principal investigator and protocol steering committee.

a. General considerations. Univariate summaries will be provided for all randomized subjects and by treatment group. Transformations will be considered for continuous variables exhibiting substantial skewness. Analyses of topiramate's effect will be conducted according to randomized treatment assignment in accordance with the intent-to-treat principle.

b. Strategy for evaluating the Co-Primary Endpoints in Aim 1. Analyses of the effects of topiramate on the co-primary endpoints will be interpreted from two perspectives. From a scientific investigational perspective, IENFD and NQOL-DN will be viewed as representing separate outcome domains, and the hypotheses of treatment effects on these outcomes will be considered conceptually distinct. Because positive findings from this early-phase trial will be subjected to conformation in a subsequent pivotal trial, the scientific hypotheses of treatment effects on the conceptually distinct co-primary endpoints will be tested on a comparison-wise basis without multiple comparison adjustment in order to enhance statistical power [74,75]. From a decision-

theoretic perspective, the results of this early-phase clinical trial will be applied to determine whether to proceed to a larger pivotal trial with a definitive clinical endpoint. Proceeding to a full-scale trial will be deemed appropriate if the present trial demonstrates that topiramate has a benefit based on either IENFD or NQOL-DN and does not have an adverse effect the other outcome. Because this choice represents a single decision point, a single global decision rule to control the risk of inappropriately proceeding to a full-scale trial will be applied. The analyses of the effect of topiramate on the IENFD and NQOL-DN as distinct endpoints are described first, followed by a global strategy for deciding whether to proceed to a full-scale trial.

c. Analysis of Co-Primary Endpoints. We hypothesize that topiramate will reduce the rate of deterioration of IENFD over the full follow-up period. Hence the primary analysis of the IENFD will compare the mean IENFD slope between the treatment and control groups under a longitudinal model with fixed effects for baseline IENFD, age, baseline BMI randomization stratification group, follow-up time (as a continuous variable), and the interaction between treatment assignment and follow-up time. Inclusion of baseline IENFD as a covariate will increase statistical power in a similar fashion as adjustment for the baseline level of the outcome in a conventional analysis of covariance. Expressed mathematically, the longitudinal model for IENFD is: $Y_{it} = \alpha_0 + Y_{i0}\,\beta_0 + \text{Age}\,\beta_1 + [\text{BMI Group}]\,\beta_2 + Y_{i0} \times \text{time}_{ij} \times \beta_3 + T_i\,\beta_4 + \text{time}_{it}\,\beta_5 + T_i \times \text{time}_{it}\,\beta_6 + \varepsilon_{it}$, $\text{Var}()=\Sigma$, $i = 1, 2, .., N$, $t = 0, 1, 2, 3$, where Y_{it} denotes the IENFD measurement for patient i at visit t, with $t = 0$ representing the baseline visit so that Y_{i0} is the baseline IENFD, T_i denotes the randomized treatment group for the ith patient (with $T_i = 1$ for the topiramate group, and $T_i = 0$ for the control group), time_{it} denotes the time of the t^{th} IENFD measurement for patient i, $T_i \times \text{time}_{it}$ denotes the treatment by time interaction, and the ε_{it} denote residuals of the IENFD measurements which are assumed to be normally distributed with a covariance matrix Σ which is described below. The coefficient β_6 represents the effect of the topirimate treatment on the mean IENFD slope over time. We will use a general unstructured covariance model for Σ [76]so that the full model represents a special case of the linear mixed model [76,77] that allows for all possible correlations among the residuals among the IENFD measurements. When the number of time points is small relative to the number of subjects as is the case for IENFD in this proposal, the general unstructured covariance model is widely used in randomized trials because it provides essentially identical statistical power to that obtained under less general covariance models while avoiding the need for post-hoc modifications to satisfy modeling assumptions[76]. Estimates of the model coefficients and standard errors will be obtained by restricted maximum likelihood estimation (RMLE)[78].

Topiramate may have direct effects on QOL that are independent of CSPN progression and which may occur shortly after treatment initiation, as well as longer term effects that result from effects of topiramate on neuropathy progression. Accordingly, the primary analysis of the NQOL-DN will compare the total mean change in the NQOL-DN from baseline to 2 years between the treatment and control groups under a longitudinal model that includes linear spline terms to allow separate mean slopes during the first 12 weeks after randomization and from 12 weeks to the end of follow-up. Age, baseline BMI group and baseline NQOL-DN will be treated as a covariates to increase statistical power. In addition to the primary comparison of the total mean change in

the NQOL-DN to 2 years, linear contrasts will be constructed to estimate the effect of the treatment on the early change in the NQOL-DN to 16 weeks, and on the longer-term NQOL-DN slope after 16 weeks. Expressed mathematically, the mixed effects model for the NQOL-DN is: $Y_{it} = \alpha_0 + Y_{i0}$ β_0 + Age β_1 + [BMI Group] $\beta_2 + Y_{i0}$ $timlo_{it}$ $\beta_3 + Y_{i0}$ $timhi_{it}$ $\beta_4 + T_i$ $\beta_5 +$ $timlo_{it}$ $\beta_6 +$ $timhi_{it}$ $\beta_7 + T_i \times$ $timlo_{it}$ $\beta_8 + T_i \times$ $timhi_{it}$ $\beta_9 + \varepsilon_{it}$, $Var(_{it})=\Sigma$, i = 1, 2, .., N, t = 0, 1, 2, …, 6, where Y_{it} denotes the NQOL-DN measurement of the i^{th} patient at visit t, $timlo_{it} = min(0, time_{it} – 16$ weeks) and $timhi_{it} = max(0, time_{it}$ – 16 weeks) represent linear spline terms in follow-up time, and the remaining terms are analogous to those defined in the model for the IENFD described above. Accounting for separate slopes in the first 16 weeks and the subsequent 80 weeks, the primary linear contrast defining the treatment effect on the mean change to 2 years is $4 \times \beta_8 + 20 \times \beta_9$. Due to the relatively large number (6) of follow-up measurement times for the NQOL-DN, an unstructured covariance model may lead to inefficient estimation[76], and a relatively parsimonious covariance model will be used to limit the number of unknown parameters to be estimated[76]. Standard covariance models to be considered include models with random intercepts and slopes combined with an autoregressive or Toeplitz covariance matrix for the residuals around the underlying trajectories[79-81]. The covariance model will be selected from a pre-specified collection of potential models by comparing BIC statistics under maximum likelihood estimation[81]. After selection of the covariance model, final statistical inferences will be performed using restricted maximum likelihood estimation as in the analyses of the IENFD outcome.

d. Missing Data. Because statistical inference is based on restricted maximal likelihood (REML) estimation, the longitudinal analyses described above will remain unbiased in the presence of missing data which follows a missing at random mechanism[82]; sensitivity analyses will be conducted using multiple imputation of missing data[83] under imputation models which incorporate auxiliary variables to account for predictors of missingness and/or the variables being analyzed beyond those in the analytic model.

e. Statistical Power for Separate Analyses of the Co-Primary Endpoints. Statistical power for IENFD was estimated by first fitting a mixed effects model to the first 2 years of follow-up for 116 subjects from the Utah Diabetic Neuropathy Study natural history cohort with baseline MNSI ≥ 3, indicating the presence of neuropathy symptoms. This cohort, as described in the preliminary data, excluded patients with longstanding neuropathy and is thus appropriate given the phenotypic similarity with CSPN. This analysis yielded variance components for IENFD trajectories over time and within-subject residuals. A design matrix was then constructed for the planned measurement schedule for the topiramate trial with IENFD measurements at baseline and weeks 32, 64 and 96 but with 4% loss-to-follow-up every 32 weeks for a total 12% loss-to-follow-up over 96 weeks. Using this design matrix and the variance components estimated from the preliminary data, 125 randomized subjects will provide 80% power with 2-sided α=0.05 to detect a difference in mean IENFD slope between the treatment and control groups of 0.47 fibers/mm/year. An effect of 0.47 fibers/mm/year represents a reduction in the mean slope from -0.68 fibers/mm/year observed in our preliminary data to -0.21 fibers/mm/year. This projected effect size is conservative given preliminary data that successful intervention may result in

improvement in IENFD rather than just slowing of its rate of decline[10,12,13]. Statistical power for the NQOL-DN was estimated based on an assumed SD for change in the NQOL-DN score over 2 years of 16.4 points, which conservatively allows for a 10% higher SD than the SD of 14.9 points reported for the change in the NQOL-DN in Boyd *et al*[24]. If the correlation between baseline and follow-up assessments is ≤ 0.60, 125 subjects with 12% loss to follow-up will provide 80% power with 2-sided α=0.05 to detect a mean difference of 7.9 points between the treatment and control groups over 96 weeks after adjustment for the baseline NQOL-DN. This represents a difference of 4.0 points per year. This power calculation is conservative, as the multiple repeated QOL measurements in the study design will provide greater precision than the simplified ANCOVA based on a single follow-up time considered in this power calculation.

f. Decision for proceeding to a full-scale trial ("Go/No-Go" Algorithm). A full-scale trial will be justified if topiramate is demonstrated to be superior to placebo for either IENFD or NQOL-DN, and non-inferior for both of these outcomes. We estimated non-inferiority margins of up to 0.50 fibers/mm/year for the IENFD slope and up to an average of 5 points per year for the NQOL-DN. A failure to proceed to the full-scale trial would be problematic if there is a treatment benefit of 0.50 fibers/mm/year for the IENFD or of an average of 5.0 points per year for the NQOL-DN and the treatment does not have an adverse effect on the other outcome. Based on these conditions, the following global decision rule was developed: Proceed to the full scale trial if either:

1. The comparison of randomized groups favors topiramate by at least 0.30 fibers/mm/yr for IENFD and favors the placebo by no more than 2.70 points per year for the NQOL-DN, *or*
2. The comparison of randomized groups favors topiramate by at least 2.97 points per year for the NQOL-DN & favors the placebo by no more than 0.22 fibers/mm/yr for the IENFD.

Given the previously stated assumptions for the analyses of IENFD and NQOL-DN as separate endpoints, and assuming a Pearson R of -0.30 between the IENFD and QOL-DN based on Boyd et al[24], numerical integration of the bivariate normal distribution implies that this global decision rule has a Type 1 error ≤ 5% for an inappropriate recommendation to proceed to a full scale trial given inferiority for at least on outcome or absence of superiority for both outcomes, and Type 2 error ≤ 18% for failure to recommend proceeding to the full scale trial when the stated criteria for superiority of at least 1 outcome and non-inferiority for both outcomes are satisfied.

g. Secondary outcomes. Treatment effects on continuous secondary outcomes which are either approximately normally distributed or can be transformed to approximate normality will be analyzed using linear mixed effect models similar to those described for IENFD and NQOL-DN. Generalized linear mixed models with outcome models appropriate to each outcome variable will be applied for ordered categorical outcomes measured at the scheduled follow-up visits and for continuous outcomes that cannot be transformed to achieve approximate normality. The treatment effect on the rate of falls will be estimated using negative binomial regression.

g. Evaluation of the clinical meaning of IENFD change. A major secondary objective of the TopCSPN study is to explore the clinical meaning of change in IENFD. TOPIRAMATE may

potentially affect NQOL-DN and other clinical endpoints (e.g., balance, fall risk) through *direct effects* that are independent of neuropathy progression (IENFD), or through *indirect effects,* which are mediated through a pathway that incorporates effects of the treatment on neuropathy progression based on IENFD. Using this conceptual framework, mechanistic information will be obtained from three types of analyses:

M1) Evaluation of the profile of treatment effects on the QOL-DN and other clinical endpoints in comparison to the treatment effect on the IENFD,

M2) Evaluation of regression coefficients relating changes in the QOL-DN and other clinical endpoints to the IENFD slope, controlling for treatment assignment,

M3) Evaluation of the "proportion of the treatment effect explained by the IENFD"[84] for the QOL-DN and other clinical endpoints.

If the treatment does not affect NQOL-DN or another clinical endpoint, the M1 and M2 analyses will provide understanding of the null effect of the treatment. The evaluation of the profile of treatment effects in M1 will be performed by plotting the estimated treatment effects on each outcome with their 95% confidence intervals. Treatment effects on continuous and categorical variables will be estimated using linear or generalized linear mixed models analogous to those described in Aim 1; the treatment effect on the rate of falls will be analyzed using negative binomial regression. Concordant effects for IENFD and a particular clinical endpoint will suggest possible mediation of the treatment effect on the clinical endpoint through IENFD, whereas discordant effects will suggest IENFD did not play a major role (i.e. was not clinically relevant). Bootstrap resampling will be used to provide 95% confidence limits for ratios of treatment effects on IENFD vs. effects on the clinical endpoints.

The treatment effect estimates in the M1 analyses represent direct comparisons of randomized groups, and hence are not subject to confounding due to the randomized trial design. This is not the case for the M2 and M3 analyses, as confounding factors that jointly influence both the intermediate variables and the NQOL-DN or other clinical endpoints will lead to biased estimates[85]. Failure to recognize this issue has led to confusion in prior applications of path analysis for evaluation of mediating factors[86]. Thus, we will seek to identify and control for baseline and follow-up factors that may potentially influence both IENFD and NQOL-DN or other clinical endpoints in the M2 and M3 analyses.[87]

The regression coefficients of the IENFD slope in the M2 analyses will provide information concerning the clinical interpretation of the IENFD slope by characterizing the difference in the 96-week change in the NQOL-DN associated with a given difference in the IENFD slope. These analyses will be carried out using a joint mixed effects model in which the NQOL-DN will be assumed to be related to the underlying random IENFD slopes. We have experience fitting similar joint models using the SAS procedure NLMIXED[88]. In the M3 analyses, the proportion of treatment effect explained (PTE) by the IENFD slope on the NQOL-DN will be obtained by first estimating the total effect of the treatment on change in the NQOL-DN to 96 weeks with adjustment for potential confounders but not the IENFD slope using a mixed effects model as

described in Aim 1, and then estimating the treatment effect on the change in the NQOL-DN that remains after controlling for the IENFD slope in a joint mixed effects model which adjusts for the IENFD slope in addition to the baseline confounders. The PTE by IENFD will be estimated by subtracting the ratio of the adjusted vs. unadjusted treatment effects from 1, and a 95% confidence interval constructed using bootstrap resampling. Similar analyses will be used to estimate the regression coefficients of the IENFD slope (for the M2 analyses) and the PTEs associated with IENFD (for the M3 analyses) for other clinical endpoints. To gain further insight into the effects of the topiramate intervention on different components of quality of life, the M2 and M3 analyses will be repeated for the five individual subscales of the NQOL-DN.

10.1. Outcomes

10.1.1. Primary Outcome (including definition)

IENFD and the validated NQOL-DN will serve as co-primary outcome measures. Rationale: The choice of endpoint measures is innovative, and validation of both measures as potential endpoints for use in a future Phase III trial is a major secondary objective of the current proposal. Most diabetic neuropathy trials use nerve conduction studies and clinical examination scales [e.g. the Neuropathy Impairment Scale Lower Limb (NIS-LL)] as primary outcome measures. However, these measures are unresponsive to change in early neuropathy[66] and their patient-based clinical meaning has not been established. Current criteria for the minimal clinically important difference in nerve conduction parameters are based on expert opinion from nearly 25 years ago[67]. IENFD was selected as an objective measure of axonal integrity. NQOL-DN was chosen as a validated neuropathy specific measure of patient reported function and QOL.

The Norfolk Quality of Life – Diabetic Neuropathy (NQOL-DN) scale: IENFD provides an essential objective biomarker of axon structure but the patient focused clinical meaning of change in IENFD has yet to be conclusively determined. Therefore, incorporation of a validated measure of patient symptoms and function is necessary. Neuropathy clinical trials should assess the impact of therapy on patient function and QOL. Pain, sensory loss, imbalance, falls and reduced mobility combine to reduce QOL. The NQOL-DN captures the full spectrum of DPN related symptoms. Data from over 1000 structured clinical interviews was reviewed for content validity in an iterative multispecialty process in order to develop the instrument [27]. 47 Items inventory DPN symptoms and their impact on function and activities of daily living. The NQOL-DN accurately distinguishes patients with and without DPN, and correlates significantly with other DPN measures[27]. The NQOL-DN is responsive to change. In an 18-week double blind crossover trial of ruboxistaurin, topiramate and placebo, total NQOL-DN improved significantly with both topiramate (12.2+/-2.76) and ruboxistaurin (-9.6+/-4.1) but not placebo (-5.6+/- 3.5)[24]. Topiramate reduces pain, and in a small clinical study was associated with increased IENFD over 18 weeks[25], suggesting an effect on small axons. By inhibiting protein kinas C-beta, Ruboxistaurin is thought to inhibit microvascular injury. Factor analysis has been used to group NQOL-DN items into 6 subscores: symptoms, autonomic, small fiber, large fiber, and activities of daily living. These different subdomains were differentially responsive to ruboxistaurin and topiramate. Topiramate treatment

was associated with a significant improvement in the small fiber and symptom subscores, which in turn significantly correlated with change in IENFD[24]. By contrast, ruboxistaurin significantly improved only the large fiber subscore. These results suggest NQOL-DN subscores are physiologically valid measures that reflect different peripheral nerve populations. NQOL-DN will serve as the co-primary outcome measure.

Intraepidermal nerve fiber density: Both CSPN and early diabetic neuropathy frequently result in loss of small unmyelinated axons before loss of larger myelinated fibers. NCS evaluate myelinated axons, but are not affected by loss of small lightly myelinated or unmyelinated axons. While unmyelinated axons may be particularly vulnerable to metabolic stress, they are also more plastic than myelinated fibers, and have more robust regenerative capacity[68]. Thus a validated biomarker of small fiber integrity would be a preferred endpoint in a CSPN clinical trial. IENFD directly reflects nociceptive axons, has demonstrated reliability equivalent to nerve conduction velocity[69], and age and gender specific normative data are available[52]. Epidermal axons are capable of regeneration in surgical and chemical axotomy models[70,71], and small studies suggest IENFD improves following intervention for diabetic neuropathy[11] and idiopathic neuropathy in the setting of prediabetes [10]. A small open label trial of topiramate in diabetic neuropathy demonstrated improved IENFD and microvascular reactivity[25] and a small randomized trial of topiramate versus ruboxistuarin or placebo demonstrated improvement in IENFD and the Total Neuropathy Score[72] among the topiramate treated participants[24].

10.1.2. Secondary Outcome(s)

Secondary outcome measures will include measures of neuropathy symptoms and signs, function and mobility, nerve conduction studies, and metabolic assessment.

i. Neuropathy symptoms:
   1. **NTSS6**[53]
   3. **Brief Pain Inventory – Diabetic Neuropathy (BPI-DN)** [54]

ii. Neuropathy signs:
   1. **Utah Early Neuropathy Scale**[48]

iii. Function and mobility
   1. **6-minute walk test (6MWT)** [56]
   2. **Timed up and Go (TUG)** [58]
   3. ABC Scale.

iv. Nerve conduction studies including Sural sensory amplitude and distal latency/conduction velocity, and Peroneal motor amplitude, distal latency, conduction velocity between the knee and ankle as described above.

v. Metabolic assessment:
   - Height, weight, BMI, waist circumference
   - Fasting glucose and insulin with calculation of the “quantitative insulin sensitivity check index” (QUICKI)[73]
   - Hemoglobin A1c
   - Fasting lipid panel

10.1.3. Exploratory Outcomes

Mechanistic Studies: This study is not designed to conclusively elucidate the precise mechanisms underlying topiramate's potential efficacy for CSPN (weight loss and resultant metabolic improvement, Na channel inhibition), but will include biomarkers specific to these putative mechanisms. DNA will be banked from subjects who agree to the optional DNA sample collection. Once blind has been broken, the genes for voltage gated sodium channels of greatest relevance to peripheral nerve function (SCN2A, 3A, 4A, 8A, 9A and 10A) will be sequenced in subsets of subjects with the greatest and least clinical improvement in order to examine for sequence variants associated with topiramate responsiveness. The relationship between baseline weight and metabolic parameters, and their improvement, and response to therapy will also be explored. Insulin sensitivity will be assessed using an indirect surrogate index (e.g. the QUICKI)[73].

10.2. Data Monitoring

All aspects of the study will be monitored by qualified individuals designated by the sponsor. Monitoring will be conducted according to Good Clinical Practice and applicable government regulations. The investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study subjects, and, if requested, agrees to assist the monitors.

Safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include contemporaneous assessment of serious adverse events.

The monitoring of subject safety and data quality will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. A Data and Safety Monitoring Board (DSMB) appointed by the NIH/NINDS will meet at 24-week intervals (or as determined by the NINDS) to review partially unblinded study data provided by the study statistician. This committee will monitor rates of adverse events and endpoints in the trial and will monitor the performance of the trial. The frequency and format of DSMB meetings, reports, and guidelines for interim analysis will be agreed upon prior to study subject enrollment.

The Protocol PI will appoint an Independent Medical Monitor (IMM) to review all adverse events, in a blinded fashion, on a periodic basis. In addition, the IMM will review all events that meet the regulatory definition of a Serious Adverse Event, upon receipt of notification via the Electronic Data Capture (EDC) system.

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device. The FDA, Office of Human Research Protection (OHRP), and NeuroNEXT CIRB requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they sign consent until 30 days following permanent discontinuation of study drug. Adverse events during the screening phase (from the time the subject signs consent until they are randomized) shall only include events related to study procedures, i.e. infection of skin biopsy site.

At that point, all ongoing AEs will be followed to resolution, but no new AEs will be recorded. The IMM/DSMB will review cumulative AEs; the frequency of this review will be determined by the IMM/DSMB in conjunction with the Protocol PI.

Each Clinical Study Site Investigator and research team (co-Investigators, research nurse, clinical trial coordinator) are responsible for identifying and reporting AEs and determining the relationship of the event to the study drug/study procedures. Aggregate reports blinded by treatment group, detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures, will be available from the DCC for review by the IMM. A separate report detailing protocol compliance will also be available monthly from the DCC for review by the Protocol PI, who will provide feedback to individual sites as needed. The Protocol Steering Committee (PSC) will advise the Protocol PI as to whether the protocol or informed consent document requires revision based on these reports.

11. DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

11.1. Data Management

Site personnel will collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The DCC is responsible for developing, testing, and managing clinical data management activities, as required, at the study sites, the CCC, and at the DCC.

The general NINDS Common Data Elements (CDE) will be used to construct data collection forms. All study data will be collected via systems created in collaboration with the DCC and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

11.1.1. Registration

Registration of subjects on this protocol will employ an interactive data system in which the clinical study site will attest to the subject's eligibility as per protocol criteria and obtain appropriate informed consent. NeuroNEXT CIRB approval for the protocol must be on file at the DCC before accrual can occur from the clinical study site.

The DCC will use a system of coded identifiers to protect subject confidentiality. When the subject is registered to participate in the study using the DCC-provided web-based registration, the system will assign a subject ID number. The unique ID code will include a protocol ID, a site ID, and a unique subject ID. To confirm the correct subject ID, the data entry system will require a second entry of the unique subject ID and compare for consistency. In this fashion, no personal identifiers would be accessible to the DCC and the data will be collected on the correctly identified subject.

11.1.2. Data Entry

Data entry will occur at the enrolling clinical study sites. Data quality assurance and analyses will be performed by the DCC. The DCC, located at the University of Iowa, will coordinate all data and statistical services for the study, as well as on-site monitoring for all participating clinical study sites.

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, online forms will be developed that contain the requisite data fields.

11.2. Role of Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with NeuroNEXT policies, and applicable Sponsor and regulatory requirements. The DCC will instruct site personnel to collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The DCC is responsible for developing, testing, and managing clinical data management activities, as required, at the clinical study sites (CSS), the CCC, and at the DCC.

The DCC is responsible for all aspects of clinical data management, and for properly instructing key study personnel (including the CCC, the CSS, and DCC staff) on how to collect, transcribe, correct and transmit the data onto CRFs or other data collection forms and logs.

The DCC is responsible for establishing procedures to ensure that clinical data management activities occur as required at the CCC, the CSS, and at the DCC.

11.3. Quality Assurance

By signing this protocol, the Sponsor and Investigator agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

11.3.1. Development of Monitoring Plan

Onsite monitoring visits will be conducted by DCC monitors according to a pre-defined Monitoring Plan. The monitoring plan will detail the frequency of on-site visits, the study data to be monitored, the review of any regulatory files, drug and supplies accountability (if applicable), documentation of the on-site visit, and the resolution process for data errors that are discovered during the visits.

All participating clinical study sites will be monitored at least once after a study initiation visit and all sites will have a close-out visit for each protocol. One on-site monitoring visit is anticipated for each clinical study site per year. All subjects will be monitored for inclusion and exclusion criteria, informed consent procedures, and adverse events. A certain percentage of data is also monitored/ source data verified against the data entered into the study database. The monitoring plan will include flexibility to revise the frequency of visits or data monitored depending on clinical study site or study related issues.

11.3.2. Site Monitoring Visits

On-site monitoring visits will be conducted by DCC monitors according to a pre-defined monitoring plan for each protocol. The goal of on-site monitoring is to analyze (review) the data as it is collected, to check the validity and integrity of the data, to verify source documentation, to ensure protection of human subjects, and to ensure protocol compliance with federal regulations. During the monitoring visit, the monitor assesses the overall status of the study, staff, and facilities to determine whether the study is being conducted per protocol and in compliance with regulatory requirements. The monitor also conducts a CRF review that includes checks of all adverse event documentation, verifies the presence of all critical correspondence and records related to investigational products and clinical supplies (if applicable), and determines if protocol violations have occurred and are documented properly. After the monitoring visit, the monitor documents the results of the monitoring visit and completes a post-visit monitoring letter that conveys any issues discovered during the visit and the need for data corrections, if appropriate. Drug and supplies accountability may also be monitored during the site visit. The DCC will work closely with the CCC to monitor and document drug distribution from the manufacturers to the clinical study sites (CSS). Each CSS will be provided with a drug accountability log which will be reviewed by the DCC monitors and reconciled with distribution logs. At the study closeout visit, the monitors confirm that appropriate data have been reviewed, source documentation has been verified, and all required documents are present in the Study Regulatory File.

11.3.3. Laboratory Data Flow

Safety Monitoring Labs: The DCC will provide laboratories with online forms and/or electronic data exchange mechanisms - depending on their capabilities and needs - to enter, update and obtain relevant data. When a blood or urine sample has been obtained, the clinical study site study coordinator will send the sample (subject ID, site ID, and protocol ID numbers will be used) to the University of Rochester central laboratory. Results will be sent via a secure system to University of Rochester laboratory with no individual-identifying information on the report. The laboratory will electronically communicate the test results to the respective clinical study sites in a secure manner. The laboratory will also transfer test results electronically to the DCC.

11.4. Adverse Experience Reporting

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization (ICH) guidelines. The Site Investigator will carefully monitor each

subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Each clinical study site's Principal Investigator and research team are responsible for identifying adverse events and reporting them through the DCC Online Adverse Event Reporting System. Investigators are also responsible for complying with NeuroNEXT CIRB's reporting requirements for all safety reports. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

An adverse event is defined as: "…an unfavorable and unintended sign, symptom, or disease associated with a subject's participation in this research trial."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

Unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks described in the protocol.

Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study.

On-line Adverse Event Reporting System

Upon entry of a serious adverse event by a site investigator, the DCC Online Adverse Event Reporting System will immediately notify the Independent Medical Monitor (IMM).

Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE) Investigators must report all other AEs within **5 working days/7 calendar days** (of learning of the event).

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study. The IMM may determine that the Serious Adverse Event requires expedited reporting to the FDA. The DCC will prepare a Medwatch safety report for submission to the FDA. If warranted, the IMM will notify the DSMB chair. The DSMB may suggest changes to the protocol or consent form to the Study Chair as a consequence of adverse events.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DCC in a timely fashion (within 5 working days). The events will be presented in tabular form and given to the IMM on a quarterly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DCC will prepare aggregate reports of all adverse events (serious/not serious, expected/unexpected and relationship to study drug) for the IMM and the DSMB on a quarterly basis or as requested. In addition, all adverse events will be coded using the MedDRA system. A separate report detailing protocol compliance will also be available from the DCC for DSMB and/or site review monthly or as requested. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

11.4.1. Definitions of Adverse Events, Suspected Adverse Drug Reactions & Serious Adverse Events

11.4.1.1. Adverse Event Collection and Reporting

Subjects will be monitored for AEs from the time they sign consent until 30 days following permanent discontinuation of study drug. Adverse events during the screening phase (from the time the subject signs consent until they are randomized) shall only include events related to study procedures, i.e. infection of skin biopsy site. If not related to study procedures, any new or worsened medical conditions reported during the screening process will be recorded in medical history.
An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately).

Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that

occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical → symptoms reported by the subject or signs detected on examination.

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures: the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the Site Investigator.

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current Investigators Brochure or package insert or described in the protocol. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the Site Investigator or Sponsor, there is a reasonable possibility that the investigational product caused the event.

11.4.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled “procedure” or a “treatment” is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the subject’s ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).

6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an *adverse* experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the Site Investigator or Sponsor, suggests a reasonable possibility that the investigational product caused the event.

The Site Investigator is responsible for classifying adverse events as serious or non-serious.

11.4.2. Assessment and Recording of Adverse Events

This study will utilize the CTCAE version 4.0 coding system for adverse event recording. Adverse events reported using CTCAE will be recoded into MedDRA terms by the DCC.

Assessment of Adverse Events

At each visit (including telephone interviews), the subject will be asked “Have you had any problems or symptoms since your last visit?” in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Investigator will determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (suspected ADR)
4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (suspected ADR)
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (suspected ADR)

Recording of Adverse Events

All clinical adverse events are recorded in the Adverse Event (AE) Log in the subject's study binder. The site should fill out the AE Log and enter the AE information into the online Adverse Event Reporting System within 5 working days of the site learning of a new AE or receiving an update on an existing AE.

Please Note: Serious Adverse Events (SAEs) must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site learning of the SAE.

Entries on the AE Log (and into the online Adverse Event Reporting System) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site being notified of the event.

- All events that meet the above criteria for Serious Adverse Events (SAEs)

All occurrences of Serious Adverse Events (SAEs) must be reported within 24 hours of discovery of the event. All other Adverse Events (AEs) must be reported within *5 business days/7 calendar days* (of discovery of the event).

Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event by a clinical site, the DCC Online Adverse Event Reporting System will immediately notify the IMM. If warranted, the IMM will notify the DSMB chair.

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The DSMB may suggest changes to the protocol or consent form to the Project PI as a consequence of adverse events. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DCC within 5 working days. The events will be presented in tabular form and given to the IMM on a quarterly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DCC will prepare aggregate reports of all adverse events (serious/not serious and expected, unexpected) for the DSMB.

12. HUMAN SUBJECTS

Documented approval from the NeuroNEXT CIRB will be obtained for all participating centers prior to clinical trial start, according to ICH GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

Evidence of training in responsible conduct of research shall be on file for each CSS PI and co-investigator.

12.1. Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the NeuroNEXT CIRB responsible for oversight of the study. A signed consent form, approved by the NeuroNEXT CIRB, will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject and this fact will be documented in the subject's record.

12.2. Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only. Clinical

information will not be released without written permission of the subject, except as necessary for monitoring by CIRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

12.3. Study Modification/Discontinuation

The study may be modified or discontinued at any time by the CIRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies of the NeuroNEXT Network and procedures developed by the NeuroNEXT Data Sharing and Publication Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission.

14. REFERENCES

1. Gregg EW, Sorlie P, Paulose-Ram R, Gu Q, Eberhardt MS, Wolz M, et al. Prevalence of lower-extremity disease in the US adult population >=40 years of age with and without diabetes: 1999-2000 national health and nutrition examination survey. Diabetes Care. 2004 Jul;27(7):1591–7.
2. Smith AG. Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. Journal of the Peripheral nervous system: JPNS. 2012 May;17 Suppl 2:15–21.
3. Smith AG, Singleton JR. The diagnostic yield of a standardized approach to idiopathic sensory-predominant neuropathy. Arch. Intern. Med. 2004 May 10;164(9):1021–5.
4. Singleton JR, Smith AG, Bromberg MB. Painful sensory polyneuropathy associated with impaired glucose tolerance. Muscle Nerve. 2001; 24:1225–8.
5. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A, KORA Study Group. Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: the MONICA/KORA Augsburg Surveys S2 and S3. Pain Med. 2009 ed. Blackwell Publishing Inc; 2009 Mar;10(2):393–400.
6. Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. Journal of Diabetes and Its Complications. 2013 May 31. PMCID: PMC3766404
7. Vincent AM, Hinder LM, Pop-Busui R, Feldman EL. Hyperlipidemia: a new therapeutic target for diabetic neuropathy. Journal of the Peripheral nervous system: JPNS. 2009 ed. 2009 Dec;14(4):257–67.
8. Davidson EP, Coppey LJ, Calcutt NA, Oltman CL, Yorek MA. Diet-induced obesity in Sprague-Dawley rats causes microvascular and neural dysfunction. Diabetes Metab Res Rev. 2010 ed. John Wiley & Sons, Ltd; 2010 May;26(4):306–18. PMCID: PMC2878284
9. Obrosova IG, Ilnytska O, Lyzogubov VV, Pavlov IA, Mashtalir N, Nadler JL, et al. High-fat diet induced neuropathy of pre-diabetes and obesity: effects of "healthy" diet

and aldose reductase inhibition. Diabetes. 2007 ed. 2007 Oct;56(10):2598–608.
10. Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care. 2006 Jun;29(6):1294–9.
11. Kludig P, Pasnoor M, Singh R, Jernigan S, Farmer K, Rucker J, et al. The Effect of Exercise on Neuropathic Symptoms, Nerve Function, and Cutaneous Innervation in People with Diabetic Peripheral Neuropathy. Journal of Diabetes and Its Complications. 2013 (26):424–9.
12. Singleton JR, Marcus RL, Jackson JE, K Lessard M, Graham TE, Smith AG. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. Ann Clin Transl Neurol. 2014 Oct;1(10):844–9. PMCID: PMC4241811
13. Singleton JR, Marcus RL, Lessard MK, Jackson JE, Smith AG. Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients. Ann. Neurol. 2014 Nov 12; n/a–n/a. PMCID: PMC4293306
14. Huang J, Han C, Estacion M, Vasylyev D, Hoeijmakers JGJ, Gerrits MM, et al. Gain-of-function mutations in sodium channel Na(v)1.9 in painful neuropathy. Brain. 2014 Jun;137(Pt 6):1627–42.
15. Argyriou AA, Cavaletti G, Antonacopoulou A, Genazzani AA, Briani C, Bruna J, et al. Voltage-gated sodium channel polymorphisms play a pivotal role in the development of oxaliplatin-induced peripheral neurotoxicity: results from a prospective multicenter study. Cancer. 2013 Oct;119(19):3570–7.
16. Channelopathies, painful neuropathy, and diabetes: which way does the causal arrow point? 2014 Oct;20(10):544–50.
17. Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS, et al. Gain of function Na(V) 1.7 mutations in idiopathic small fiber neuropathy. Ann. Neurol. 2011 ed. 2011 May 20;71(1):26–39.
18. Bennett DLH. Voltage-gated sodium channel mutations and painful neuropathy: Na(v)1.9 joins the family. Brain. 2014 Jun;137(Pt 6):1574–6.
19. Coomans CP, Geerling JJ, van den Berg SAA, van Diepen HC, Garcia-Tardon N, Thomas A, et al. The insulin sensitizing effect of topiramate involves KATP channel activation in the central nervous system. Br J Pharmacol. 2013 Oct;170(4):908–18. PMCID: PMC3799603
20. El-Abhar HS, Schaalan MF. Topiramate-induced modulation of hepatic molecular mechanisms: an aspect for its anti-insulin resistant effect. Pereira RI, editor. PLoS ONE. 2012;7(5):e37757. PMCID: PMC3359316
21. Kramer CK, Leitao CB, Pinto LC, Canani LH, Azevedo MJ, Gross JL. Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. Obes Rev. 2011 May;12(5):e338–47.
22. Raskin P, Donofrio PD, Rosenthal NR, Hewitt DJ, Jordan DM, Xiang J, et al. Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. Neurology. 2004 Sep 14;63(5):865–73.
23. Donofrio PD, Raskin P, Rosenthal NR, Hewitt DJ, Jordan DM, Xiang J, et al. Safety and effectiveness of topiramate for the management of painful diabetic peripheral

neuropathy in an open-label extension study. Clin Ther. 2005 Sep;27(9):1420–31.
24. Boyd A, Casselini C, Vinik E, Vinik A. Quality of life and objective measures of diabetic neuropathy in a prospective placebo-controlled trial of ruboxistaurin and topiramate. J Diabetes Sci Technol. 2011 May;5(3):714–22. PMCID: PMC3192638
25. Boyd AL, Barlow PM, Pittenger GL, Simmons KF, Vinik AI. Topiramate improves neurovascular function, epidermal nerve fiber morphology, and metabolism in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2010; 3:431–7. PMCID: PMC3047986
26. Lopes LS, Pereira SS, Silva LL, Figueiredo KA, Moura BA, Almeida FRC, et al. Antinociceptive effect of topiramate in models of acute pain and diabetic neuropathy in rodents. Life Sci. 2009 Jan 16;84(3-4):105–10.
27. Vinik EJ, Hayes RP, Oglesby A, Bastyr E, Barlow P, Ford-Molvik SL, et al. The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. Diabetes Technol. Ther. 2005 Jun;7(3):497–508.
28. Vinik EJ, Paulson JF, Ford-Molvik SL, Vinik AI. German-translated Norfolk quality of life (QOL-DN) identifies the same factors as the English version of the tool and discriminates different levels of neuropathy severity. J Diabetes Sci Technol. 2008 Nov;2(6):1075–86. PMCID: PMC2769831
29. Ben-Menachem E, Axelsen M, Johanson EH, Stagge A, Smith U. Predictors of weight loss in adults with topiramate-treated epilepsy. Obes. Res. 2003 Apr;11(4):556–62.
30. Caricilli AM, Penteado E, de Abreu LL, Quaresma PGF, Santos AC, Guadagnini D, et al. Topiramate treatment improves hypothalamic insulin and leptin signaling and action and reduces obesity in mice. Endocrinology. 2012 Sep;153(9):4401–11.
31. Abo-Elmatty DM, Zaitone SA. Topiramate induces weight loss and improves insulin sensitivity in dietary obese rats: comparison to sibutramine. Eur Rev Med Pharmacol Sci. 2011 Oct;15(10):1187–95.
32. Liang Y, Chen X, Osborne M, DeCarlo SO, Jetton TL, Demarest K. Topiramate ameliorates hyperglycaemia and improves glucose-stimulated insulin release in ZDF rats and db/db mice. Diabetes Obes Metab. 2005 Jul;7(4):360–9.
33. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N. Engl. J. Med. 2003rd ed. 2003 Jan 30;348(5):383–93.
34. Chong MS, Libretto SE. The rationale and use of topiramate for treating neuropathic pain. Clin J Pain. 2003 Jan;19(1):59–68.
35. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med. 2005 Sep-Oct;6(5):346–56.
36. Zhang J-L, Yang J-P, Zhang J-R, Li R-Q, Wang J, Jan J-J, et al. Gabapentin reduces allodynia and hyperalgesia in painful diabetic neuropathy rats by decreasing expression level of Nav1.7 and p-ERK1/2 in DRG neurons. Brain Res. 2013 Feb 1;

1493:13–8.
37. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit. Rev. Oncol. Hematol. 2012 Apr;82(1):51–77.
38. Zuliani V, Rivara M, Fantini M, Costantino G. Sodium channel blockers for neuropathic pain. Expert Opin Ther Pat. 2010 Jun;20(6):755–79.
39. Erdoğan C, Yücel M, Akgün H, Kaşkç T, Semai Bek V, Gökçil Z. Effects of topiramate on peripheral nerve excitability. J Clin Neurophysiol. 2012 Jun;29(3):268–70.
40. Smith SC, Lamping DL, Maclaine GDH. Measuring health-related quality of life in diabetic peripheral neuropathy: a systematic review. Diabetes Res. Clin. Pract. 2012 Jun; 96(3):261–70.
41. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: A randomized, controlled trial. Neurology. 2012 Aug 21;79(8):785–92. PMCID: PMC4098875
42. Shun CT, Chang YC, Wu HP, Hsieh SC, Lin WM, Lin YH, et al. Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. Brain. 2004 ed. 2004 Jul;127(Pt 7):1593–605.
43. Periquet MI, Novak V, Collins MP, Nagaraja HN, Erdem S, Nash SM, et al. Painful sensory neuropathy prospective evaluation using skin biopsy. Neurology. 1999; 53:1641–7.
44. Smith AG, Tripp C, Singleton JR. Skin biopsy findings in patients with neuropathy associated with diabetes and impaired glucose tolerance. Neurology. 2001; 57:1701.
45. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010 ed. 2010 Oct;33(10):2285–93. PMCID: PMC2945176
46. The Expert Panel on Detection EATOHBCIA. The Third Report of the ATP III. National Institutes of Health National Heart Lung and Blood Institute, Bethesda Maryland. 2001; NIH publication 01-3670: https://www.nhlbi.nih.gov–guidelines–cholesterol–index.htm.
47. England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology. 2008 ed. 2009 Jan 13;72(2):185–92.
48. Singleton JR, Bixby B, Russell JW, Feldman EL, Peltier A, Goldstein J, et al. The Utah Early Neuropathy Scale: a sensitive clinical scale for early sensory predominant neuropathy. Journal of the Peripheral nervous system: JPNS. 2008 ed. Blackwell Publishing Inc; 2008 Sep;13(3):218–27.
49. Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical

samples. Assessment. 2001 Dec;8(4):443–54.
50. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2005 Jan 25;64(2):199–207.
51. Bril V, Ellison R, Ngo M, Bergstrom B, Raynard D, Gin H. Electrophysiological monitoring in clinical trials. Roche Neuropathy Study Group. Muscle Nerve. 1998 Nov;21(11):1368–73.
52. Lauria G, Bakkers M, Schmitz C, Lombardi R, Penza P, Devigili G, et al. Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. Journal of the Peripheral nervous system: JPNS. 2010 ed. 2010 Sep;15(3):202–7.
53. Bastyr EJ, Price KL, Bril V, MBBQ Study Group. Development and validity testing of the neuropathy total symptom score-6: questionnaire for the study of sensory symptoms of diabetic peripheral neuropathy. Clin Ther. 2005 Aug;27(8):1278–94.
54. Zelman DC, Gore M, Dukes E, Tai K-S, Brandenburg N. Validation of a modified version of the brief pain inventory for painful diabetic peripheral neuropathy. J Pain Symptom Manage. 2005 Apr;29(4):401–10.
55. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann. Acad. Med. Singap. 1994 Mar; 23(2):129–38.
56. Beriault K, Carpentier AC, Gagnon C, Menard J, Baillargeon J-P, Ardilouze J-L, et al. Reproducibility of the 6-minute walk test in obese adults. Int J Sports Med. 2009 Oct;30(10):725–7.
57. Tuttle LJ, Sinacore DR, Mueller MJ. Intermuscular adipose tissue is muscle specific and associated with poor functional performance. J Aging Res. 2012; 2012:172957. PMCID: PMC3361226
58. Herman T, Giladi N, Hausdorff JM. Properties of the “timed up and go” test: more than meets the eye. Gerontology. 2011;57(3):203–10. PMCID: PMC3094679
59. Vaz MM, Costa GC, Reis JG, Junior WM, Albuquerque de Paula FJ, Abreu DC. Postural control and functional strength in patients with type 2 diabetes mellitus with and without peripheral neuropathy. Arch Phys Med Rehabil. 2013 Dec;94(12):2465–70.
60. Jernigan SD, Pohl PS, Mahnken JD, Kluding PM. Diagnostic accuracy of fall risk assessment tools in people with diabetic peripheral neuropathy. Phys Ther. 2012 Nov;92(11):1461–70. PMCID: PMC3488267
62. Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol. 2010 ed. 2010 Jul;17(7):903–12–e44–9.
63. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified

neuropathies yields improved diagnosis. Ann. Neurol. 1981; 10:222–6.
64. Thienel U, Neto W, Schwabe SK, Vijapurkar U, Topiramate Diabetic Neuropathic Pain Study Group. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol. Scand. 2004 Oct;110(4):221–31.
65. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev. John Wiley & Sons, Ltd; 2013;6:CD010610.
66. Dyck PJ, Norell JE, Tritschler H, Schuette K, Samigullin R, Ziegler D, et al. Challenges in design of multicenter trials: end points assessed longitudinally for change and monotonicity. Diabetes Care. 2007 ed. 2007 Oct;30(10):2619–25.
67. Dyck P, OBrien P. Meaningful degrees of prevention or improvement of nerve conduction in controlled clnical trials of diabetic neuropathy. Diabetes Care. 1989; 12:649–52.
68. Griffin JW, Thompson WJ. Biology and pathology of nonmyelinating Schwann cells. Glia. 2008 Nov 1;56(14):1518–31.
69. Smith AG, Howard JR, Kroll R, Ramachandran P, Hauer P, Singleton JR, et al. The reliability of skin biopsy with measurement of intraepidermal nerve fiber density. J. Neurol. Sci. 2005 Jan 15;228(1):65–9.
70. Rajan B, Polydefkis M, Hauer P, Griffin JW, McArthur JC. Epidermal reinnervation after intracutaneous axotomy in man. J Comp Neurol. 2003 Feb 24;457(1):24–36.
71. Polydefkis M, Hauer P, Sheth S, Sirdofsky M, Griffin JW, McArthur JC. The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. Brain. 2004 Jul;127(Pt 7):1606–15.
72. Cornblath DR, Chaudhry V, Carter K, Lee D, Seysedadr M, Miernicki M, et al. Total neuropathy score: validation and reliability study. Neurology. 1999 Nov 10;53(8):1660–4.
73. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am. J. Physiol. Endocrinol. Metab. 2008 Jan; 294(1):E15–26.
74. Goodman SN. Multiple Comparisons, Explained. Am. J. Epidemiol. Oxford University Press; 1998 May 1;147(9):807–12.
75. SAS/STAT 13.2 User's Guide.
76. Molenberghs G, Thijs H, Jansen I, Beunckens C, Kenward MG, Mallinckrodt C, et al. Analyzing incomplete longitudinal clinical trial data. Biostatistics. Oxford University Press; 2004 Jul;5(3):445–64.
77. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. John Wiley & Sons; 2012.
78. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. Springer Science & Business Media; 2009.
79. Littell RC, Pendergast J, Natarajan R. Modelling covariance structure in the analysis of repeated measures data. Stat Med. 2000 Jul 15;19(13):1793–819.
80. Kincaid C. Guidelines for selecting the covariance structure in mixed model analysis,

paper 198-30 in Proceedings of the Thirtieth Annual SAS Users Group …. Inc; 2005.
81. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. Springer; 2000.
82. Multiple imputation: a primer.
83. Schafer JL. Multiple imputation: a primer. Stat Methods Med Res. SAGE Publications; 1999 Mar;8(1):3–15.
84. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Stat Med. 1992 Jan 30;11(2):167–78.
85. Rubin DE. Direct and indirect causal effects via potential outcomes. Scan J Statistics. 32:161–70.
86. Frangakis CE, Rubin DB. Principal stratification in causal inference. Biometrics. 2002 Mar;58(1):21–9. PMCID: PMC4137767
87. Joffe MM, Greene T. Related causal frameworks for surrogate outcomes. Biometrics. Blackwell Publishing Inc; 2009 Jun;65(2):530–8.
88. SAS Institute Inc. SAS/STAT 13.2 User's Guide.
89. Myers, A. M., Fletcher, P. C., Myers, A. H., & Sherk, W. (1998). Discriminative and evaluative properties of the activities-specific balance confidence (ABC) scale. *J Gerontol a Biol Sci Med Sci*, *53*(4), M287–94.
90. Topolski, T. D., LoGerfo, J., Patrick, D. L., Williams, B., Walwick, J., & Patrick, M. B. (2006). The Rapid Assessment of Physical Activity (RAPA) among older adults. *Preventing Chronic Disease*, *3*(4), A118.

15. Appendix A

Schedule of Assessments: Topiramate as a Disease Modifying Therapy for CSPN

Tests and Evaluations[1]	Screening	Baseline	W16	W32	W48	W64	W80	W96	Safety Assessment	Early Termination
Visit Number	1	2	3	4	5	6	7	8	9	ET
Telephone Calls [2]		X²	X²	X²	X²	X²	X²			
Informed Consent	X									
Inclusion/exclusion criteria	X	X								
Medical History	X									
Complete Physical Examination	X							X	X	X
Abbreviation physical Examination (including visual field and fall risk assessment)		X	X	X	X	X	X			
Interval Medical History		X	X	X	X	X	X	X	X	X
Vital Signs (including height[3], weight, and BMI)	X	X	X	X	X	X	X	X	X	X
Waist Circumference	X		X	X	X	X	X	X	X	X
Nerve Conduction Studies		X		X		X		X		X
Distal Thigh Skin Biopsy		X		X		X		X		X
Topiramate Level		X		X		X		X		X
Serum B12 and immunofixation	X									
Fasting glucose[4], insulin, and lipid panel, and hemoglobin A1c	X			X		X		X		X
2-HR oral glucose tolerance test	X			X		X		X		X
Basic metabolic panel and complete blood count	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X		X	X	X	X	X			

[1] Baseline visit will occur within 30 days of screening. All follow-up visits must occur within ± 7 days.
[2] Study coordinators will call each subject at least once per month to encourage participation and minimize dropout risk.
[3] Height at screening visit only.
[4] Fasting glucose is the pre-glucola/dextrose sample for the OGTT (gray top).

Urine pregnancy test		X								
Functional and mobility testing (6MWT, TUG, ABC Scale)		X		X		X		X		X
Randomization		X								
Study drug dispensing		X	X	X	X	X	X			
Study drug reconciliation			X	X	X	X	X	X		X
Neuropathy symptom scales (NTSS-6, BPI-DN)		X	X	X	X	X	X	X		X
NQOL-DN	X		X	X	X	X	X	X		X
UENS	X		X	X	X	X	X	X		X
C-SSRS	X	X	X	X	X	X	X	X	X	X
RAPA		X		X		X		X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse event review	X[5]	X	X	X	X	X	X	X	X	X
ECG	X									
DNA sample		X								

[5] AEs to be collected at screening **only** for events related to study procedures (e.g., skin biopsy)