A Single-Arm Pilot Study of the Feasibility and Efficacy of Electro-Acupuncture in Subjects with Chemotherapy-Induced Peripheral Neuropathy

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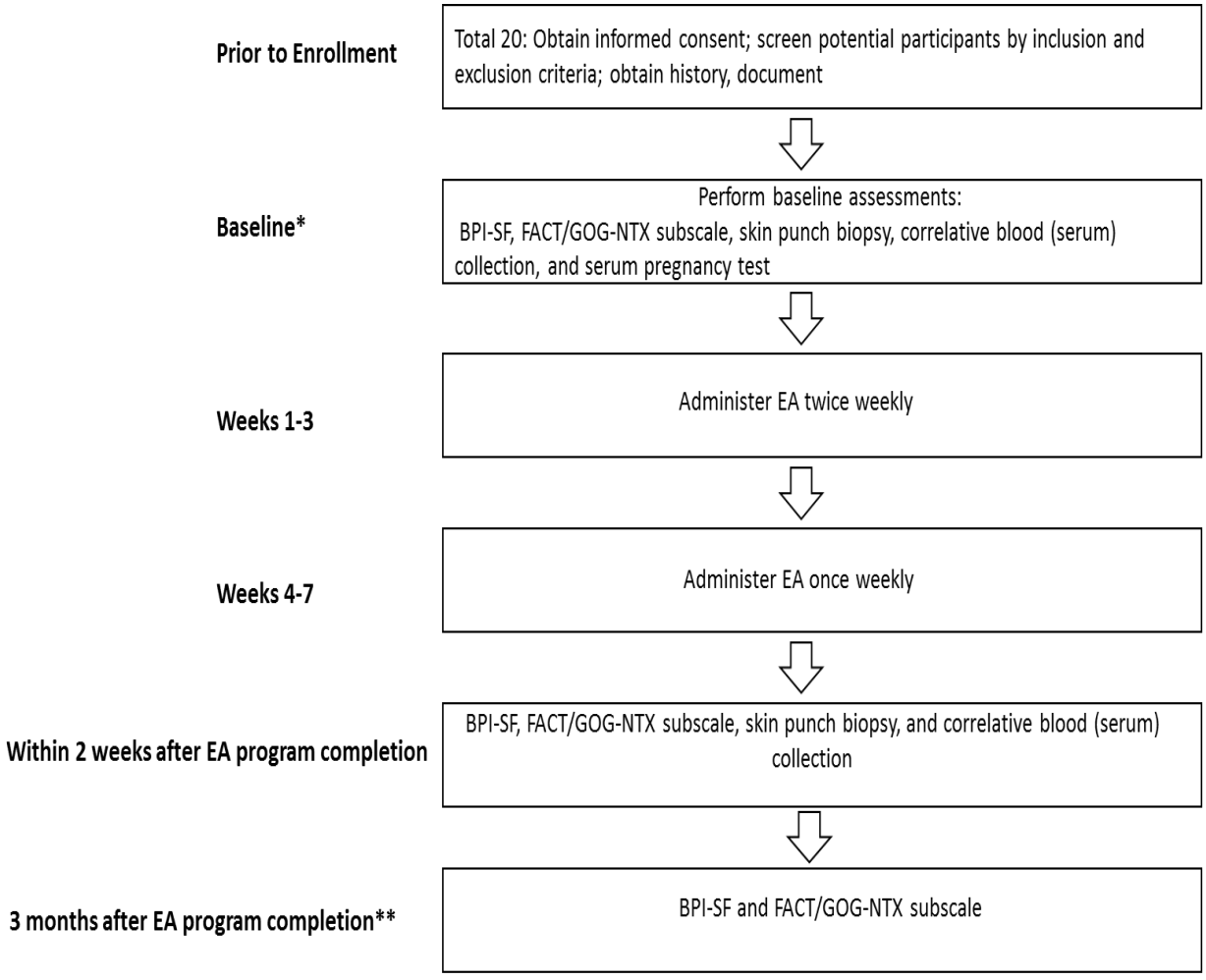
1.0 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Single-Arm Pilot Study of the Feasibility and Efficacy of Electro-Acupuncture in Subjects with Chemotherapy-Induced Peripheral Neuropathy
Study Description:	This study will determine the feasibility and efficacy of a 10-treatment electro-acupuncture (EA) program in subjects with chemotherapy-induced peripheral neuropathy (CIPN). We hypothesize that EA will be a feasible and effective therapy for CIPN.
Objectives:	Primary Objective**:** • To determine the feasibility of a 10-treatment EA program in subjects with CIPN. Secondary Objectives: • To determine the change in neuropathic pain after a 10-treatment EA program in subjects with CIPN, as assessed by the Brief Pain Inventory-Short Form (BPI-SF). • To determine the change in quality of life after a 10-treatment EA program in subjects with CIPN, as assessed by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) subscale. Exploratory Objectives: • To measure the change in intraepidermal nerve fiber (IENF) density after a 10-treatment EA program in subjects with CIPN. • To measure the changes in serum levels of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6 after a 10-treatment EA program in subjects with CIPN.
Endpoints:	Primary Endpoint**:** • Feasibility of a 10-treatment EA program in subjects with CIPN. Secondary Endpoints: • Change in worst BPI-SF pain score before and after a 10-treatment EA program in subjects with CIPN. • Change in FACT/GOG-NTX subscale score before and after a 10-treatment EA program in subjects with CIPN. Exploratory Endpoints: • Change in IENF density before and after a 10-treatment EA program in subjects with CIPN.

	• Changes in serum levels of inflammatory markers including ESR, CRP, TNF-α, IL-1, and IL-6 before and after a 10-treatment EA program in subjects with CIPN.
Study Population:	Twenty male or female subjects aged ≥18 years with CIPN
Phase:	N/A
Description of Site Enrolling Participants:	This will be a single-center study conducted at Houston Methodist Hospital, Houston Methodist Sugarland and Houston Methodist West Hospital.
Description of Study Intervention:	EA is a non-pharmacologic treatment that combines traditional acupuncture with electrical stimulation. EA will be administered for a total of 10 treatments over a 7-week period. EA will be done twice weekly for Weeks 1−3 and then weekly for Weeks 4−7. Each treatment will take approximately 30 minutes.
Study Duration:	Approximately 3 years
Participant Duration:	Approximately 5 months (7 weeks of treatment and 3 months of follow-up)

1.2 SCHEMA



*Within 4 weeks of starting the 10-treatment EA program
**A window of +/- 4 weeks is allowed.

BPI-SF = Brief Pain Inventory-Short Form; EA = electro-acupuncture; FACT/GOG-NTX = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Procedure	Baseline[a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Within 2 weeks after EA program completion	3 months after EA program completion[b]
ECOG Performance Status	X									
Serum Pregnancy Test (β-HCG)[c]	X									
BPI-SF[d]	X								X	X
FACT/GOG-NTX Subscale[e]	X								X	X
Correlative Blood (Serum) Collection[f]	X								X	
EA[g]		X	X	X	X	X	X	X		

β-hCG = beta-human chorionic gonadotropin; BPI-SF = Brief Pain Inventory-Short Form; CRP = C-reactive protein; EA = electro-acupuncture; ECOG = Eastern Cooperative Oncology Group; FACT/GOG-NTX = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; ESR = erythrocyte sedimentation rate; IENF = intraepidermal nerve fiber; IL = interleukin; PGP9.5 = protein gene product 9.5; TNF-α = tumor necrosis factor-alpha.

a. Within 4 weeks of starting the 10-treatment EA program.
b. A window of ± 4 weeks is allowed.
c. For women of childbearing potential, the results of a serum β-hCG pregnancy test must be negative within 14 days prior to the start of the 10-treatment EA program.
d. The BPI-SF will be completed at baseline, within 2 weeks after EA program completion, and 3 months after EA program completion to assess change in neuropathic pain.
e. The FACT/GOG-NTX will be completed at baseline, within 2 weeks after EA program completion, and 3 months after EA program completion to assess change in quality of life.
f. Blood (serum) samples will be collected at baseline and within 2 weeks after EA program completion for assessment of correlative inflammatory markers (ESR, CRP, TNF-α, IL-1, and IL-6).
g. Ten EA treatments will be administered over a 7-week period; EA will be done twice weekly for Weeks 1−3 and once weekly for Weeks 4−7.

2.0 INTRODUCTION

2.1 BACKGROUND

2.1.1 CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Chemotherapy-induced peripheral neuropathy (CIPN) is a very common and sometimes dose-limiting side effect of cancer treatment. CIPN is estimated to occur in up to 40% of patients undergoing chemotherapy, with its incidence increasing in patients being treated with multiple agents.[1,2] The incidence of CIPN varies depending on chemotherapy drug, dose, and treatment duration.[3] Multiple classes of chemotherapeutics are strongly associated with CIPN occurrence, including platinum compounds (cisplatin, oxaliplatin, and carboplatin), microtubule inhibitors (vincristine, paclitaxel, and ixabepilone), and proteasome inhibitors (bortezomib). The symptoms of CIPN vary according to the type of nerve fibers affected and can include numbness, tingling, stinging, pain, weakness, or burning in the lower extremities and hands; altered pain threshold; changes in temperature sensitivity; muscle spasms and muscle wasting; and loss of muscle dexterity and strength. These symptoms can lead to decreased functional capacity (loss of mobility and increased fall risk) and quality of life, especially in older patients in whom CIPN is more prevalent and severe.[4] Although CIPN symptoms generally improve over time, 30% of patients experience persistent neuropathic pain for ≥6 months after chemotherapy completion.[5]

2.1.2 TREATMENT OPTIONS FOR CIPN

There are few effective treatment options for CIPN. The American Society of Clinical Oncology (ASCO) guidelines recommend the use of the selective serotonin and norepinephrine reuptake inhibitor duloxetine for the treatment of CIPN.[2] This recommendation is based on a double-blind, placebo-controlled randomized trial showing duloxetine to be more effective than placebo in reducing CIPN pain.[6] However, drug interactions (e.g., other antidepressants and tamoxifen), cost, and intolerability limit duloxetine use. As many patients, especially those with chronic pain, prefer to not take medication over a long-term period, duloxetine use is also characterized by poor adherence rates (as low as 30%).[7]

2.1.3 ELECTRO-ACUPUNCTURE FOR CIPN

Electro-acupuncture (EA) is a non-pharmacologic treatment that combines traditional acupuncture with electrical stimulation and involves passing a small electrical current between pairs of acupuncture needles. Electrical stimulation has been found to enhance the analgesic effect of acupuncture.[8] The mechanisms underlying acupuncture-mediated analgesia are unclear. Studies have suggested that the analgesic effect of acupuncture is related to a reduction in inflammation. In subjects with asthma, allergic rhinitis, and rheumatoid arthritis, acupuncture decreased the levels of inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-10, which was associated with symptom improvement.[9,10]

In randomized, placebo-controlled trials, traditional acupuncture and EA have been proven to be beneficial for the treatment of diabetic peripheral neuropathy.[11-13] Pilot studies have also demonstrated the promising activity of acupuncture and EA for the treatment of human

immunodeficiency virus-related peripheral neuropathy.[14,15] Acupuncture and EA have been shown to be efficacious in patients with CIPN. In a prospective case series, 5 subjects with CIPN treated with acupuncture (two 6-week cycles) showed improvement in pain score; this improvement persisted for 6 months of follow-up in 4 of the 5 patients.[16] Side effects were not observed. In a retrospective case series, 82% (14/18) of subjects reported an improvement in CIPN symptoms after completion of 6 weekly acupuncture sessions.[17] A controlled randomized pilot study demonstrated the superiority of acupuncture over cobamamide (active form of vitamin B12) in alleviating CIPN symptoms (66.7% [20/30] vs. 40.0% [12/30]; $P < 0.05$).[18] A Phase II study evaluated the safety and efficacy of acupuncture-like transcutaneous nerve stimulation delivered twice weekly over 6–8 weeks in 27 subjects with CIPN.[19] Modified total neuropathy scores were significantly ($P < 0.001$) improved at the 6-month follow-up compared with baseline, indicating an improvement in CIPN symptoms. A significant reduction in numbness scores from baseline to the 6-month follow-up was also observed. *P* values for numbness scores in palm, finger, foot, and toe were 0.0066, 0.0014, 0.0016, and 0.004, respectively. There were no significant reported side effects. Three subjects reported a moderate aching discomfort at the stimulation sites during treatments, and 1 subject developed a mild skin rash at one of the stimulation sites. A non-randomized pilot study demonstrated the feasibility and efficacy of EA for the treatment of thalidomide/bortezomib-induced peripheral neuropathy in 27 subjects with multiple myeloma.[20] Subjects received 20 EA sessions at 2–3 times per week over 9 weeks. The drop-out rate was low at 30% (8/27). Among the 19 evaluable subjects, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) subscale mean (standard deviation) scores improved significantly between baseline (20.8 [9.6]) and all subsequent time points: Week 4: 16.7 (9.4), $P = 0.02$; Week 9: 9.9 (5.6), $P < 0.0001$; and Week 13 (1-month follow-up): 13.2 (8.5), $P = 0.0002$. Significant improvements were also observed in the Brief Pain Inventory-Short Form (BPI-SF) mean scores (pain severity, pain interference, and worst pain in last 24 hours) at all time points. Furthermore, timed functional test scores were significantly better at Week 13 (coin test: 10.0 [7.4] vs. 5.6 [1.9], $P < 0.0001$; button test: 96.1 [144.4] vs. 54.9 [47.3], $P < 0.0001$; walking test: 21.6 [10.0] vs. 17.2 [7.7], $P = 0.003$; postural stability: 1.0 [0.6] vs. 0.8 [0.4], $P = 0.02$). No adverse events (AEs) related to acupuncture were reported. Together, these studies highlight the potential therapeutic value of EA for the treatment of CIPN.

2.2 STUDY RATIONALE

CIPN is a common and disabling side effect of chemotherapy. In the majority of cancer patients, CIPN is only partially reversible and can persist long after treatment completion. Currently, the antidepressant duloxitene is the only recommended treatment for CIPN. EA is a safe, minimally invasive procedure that has shown promise as a treatment option for CIPN.[16-22] Our hypothesis is that EA will be a feasible and effective therapy for cancer patients suffering from CIPN. Data originating from this study will be instrumental in laying the groundwork for establishing EA as a treatment modality for CIPN, provide important insights into the underlying mechanisms of EA, and provide a foundation for a future large-scale randomized clinical trial.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

EA is a safe, minimally invasive procedure with few to no side effects.[19,20,22] Mild side effects include aching discomfort and skin rash at the stimulation sites during treatment and minor discomfort, swelling, and bruising after acupuncture needle withdrawal. EA will be administered by a certified, licensed acupuncture practitioner who is a member of the American College of Acupuncture & Oriental Medicine.

2.3.2 KNOWN POTENTIAL BENEFITS

EA has been shown to improve CIPN symptoms as well as patient quality of life[19,20] and therefore, may offer a safe non-pharmacological treatment option for cancer patients with CIPN.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

CIPN is a common and devastating side effect of chemotherapy treatment that negatively impacts patient quality of life. Duloxetine is the only pharmacologic therapy recommended in the ASCO clinical practice guidelines for the treatment of CIPN in cancer patients. Thus, identification of effective therapies for CIPN remains a significant unmet need. EA has a low toxicity profile and has demonstrated promising efficacy against CIPN.[19, 20,22] Results from this study will provide the basis for a future, large-scale randomized clinical trial to establish the potential therapeutic role of EA in the treatment of CIPN. Overall, the anticipated benefit-risk profile highly supports the investigation of EA in subjects with CIPN.

3.0 3OBJECTIVES AND ENDPOINTS

Primary Objective:

- To determine the feasibility of a 10-treatment EA program in subjects with CIPN.

Secondary Objectives:

- To determine the change in neuropathic pain after a 10-treatment EA program in subjects with CIPN, as assessed by the BPI-SF (see Section 13.1).

- To determine the change in quality of life after a 10-treatment EA program in subjects with CIPN, as assessed by the FACT/GOG-NTX subscale (see Section 13.2).

Exploratory Objectives:

- To measure the change in intraepidermal nerve fiber (IENF) density after a 10-treatment EA program in subjects with CIPN.

- To measure the changes in serum levels of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), TNF-α, IL-1, and IL-6 after a 10-treatment EA program in subjects with CIPN.

Primary Endpoint**:**

- Feasibility of a 10-treatment EA program in subjects with CIPN.

Secondary Endpoints:

- Change in worst BPI-SF pain score before and after a 10-treatment EA program in subjects with CIPN.

- Change in FACT/GOG-NTX subscale score before and after a 10-treatment EA program in subjects with CIPN.

Exploratory Endpoints:

- Change in IENF density before and after a 10-treatment EA program in subjects with CIPN.

- Changes in serum levels of inflammatory markers including ESR, CRP, TNF-α, IL-1, and IL-6 before and after a 10-treatment EA program in subjects with CIPN.

4.0 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-arm pilot study assessing the feasibility and efficacy of EA in 20 subjects with CIPN. The primary objective is to determine the feasibility of a 10-treatment EA program in subjects with CIPN. Feasibility will be defined as ≥15 patients completing ≥8 EA treatments. Secondary objectives include change in neuropathic pain and quality of life before and after EA treatment. An exploratory correlative analysis of mechanistic biomarkers will also be performed.

4.2 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the SOA (Section 1.3).

The end of the study is defined as completion of the last visit or procedure shown in the SOA in the trial globally.

5.0 STUDY POPULATION

Twenty male or female subjects with CIPN will be prospectively enrolled to complete a 10-treatment EA program.

5.1 INCLUSION CRITERIA

- Male or female aged ≥18 years;

- Received curative-intent chemotherapy (i.e., paclitaxel, docetaxel, nab-paclitaxel, carboplatin, oxaliplatin, vinorelbine, ixabepilone, or vincristine) ≥3 months prior to the start of EA treatment;

- Persistent Grade ≥2 peripheral neuropathy in the fingers or toes according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0;
- Eastern Cooperative Oncology Group performance status of ≤2 (see Section 13.3);
- Willing and able to provide written informed consent for the study.

5.2 EXCLUSION CRITERIA

- Documented medical history of neuropathy resulting from nerve compression (e.g., carpal tunnel syndrome, radiculopathy, or spinal stenosis);
- Severe coagulopathy or bleeding disorder, per the treating physician's discretion;
- Presence of cellulitis or other skin infection or condition that would preclude placement of acupuncture needles into the hands or feet;
- Diabetes unless Hgb A1c <7.5%;
- Unstable cardiac disease;
- Pacemaker;
- Metal plates;
- Known psychiatric disorder that would interfere with cooperation with the requirements of the study;
- Pregnant.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 CONTRACEPTION

Female subjects of reproductive potential must agree to avoid becoming pregnant while receiving the study intervention by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use acceptable contraception during heterosexual activity.

Acceptable methods of contraception are:
Single method (one of the following is acceptable):

- intrauterine device
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Subjects should be informed that the study intervention may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of trial therapy initiation throughout the study period.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

6.0 STUDY INTERVENTION

6.1 STUDY INTERVENTION DESCRIPTION

EA is a non-pharmacologic treatment that combines traditional acupuncture with electrical stimulation and involves passing a small electrical current between pairs of acupuncture needles.

6.2 STUDY INTERVENTION ADMINISTRATION

EA will be administered for a total of 10 treatments over a 7-week period. EA will be done twice weekly for Weeks 1−3 and then weekly for Weeks 4−7. Each treatment will take approximately 30 minutes. Subjects will receive free parking vouchers for treatment visits scheduled at the Houston Methodist Hospital.

EA will be administered by a certified, licensed acupuncture practitioner who is a member of the American College of Acupuncture & Oriental Medicine. The EA acupuncture point protocol to be

used in this study is shown in Table 1 and was developed based on a standard Traditional Chinese Medicine protocol for energy (*qi*) and blood deficiency and stagnation and the acupuncture points proposed by the American College of Acupuncture & Oriental Medicine. All subjects will undergo needle insertion at all points. A stainless steel disposable acupuncture needle (Spirit 0.22×25 mm 34# 1.0" needle) will be inserted into the skin to the depth (approximately 3–4 mm) needed to elicit *de qi*. *De qi* is the term used to describe a sensation characteristic of acupuncture needling (i.e., a dull or achy sensation of soreness). Selected acupuncture points will be attached to two leads connected to an electro-stimulator (Yingdi KWD-808 Multi-Purpose Transcutaneous Simulator Device) that will generate 2 Hz of mixed pulsatile intervals for a total of 20 minutes. Electrical nodes will be placed bilaterally on points LV3 and LI4, with a positive node at point LV3.

Table 1: EA Point Protocol

Position	Point	Location
Hand	LI4 × 2	On the dorsum of the hand, between the first and second metacarpal bones, in the middle of the second metacarpal bone on the radial side
Hand	SI3 × 2	When a loose fist is made, the point is on the ulnar aspect of the hand, proximal to the fifth metacarpophalangeal joint, at the end of the transverse crease of the metacarpophalangeal joint, at the junction of the red and white skin
Foot	LV3 × 2	On the dorsum of the foot, in the depression proximal to the 1st metatarsal space
Leg	ST36 × 2	On the anterior aspect of the lower leg, 3 cun below ST35, one finger breadth from the anterior crest of the tibia
Foot	ST44 × 2	On the dorsum of the foot proximal to the web margin between the second and third metatarsal toes at the junction of the red and white skin
Ankle	K3 × 2	In the depression midway between the tip of the medial malleolus and the attachment of the Achilles tendon

7.0 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a subject from the study for the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- If any clinical AE or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The subject has a confirmed positive serum pregnancy test

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 PAIN AND QUALITY OF LIFE ASSESSMENTS

To assess neuropathic pain and quality of life, each subject will be asked to complete the BPI-SF and FACT/GOG-NTX subscale, respectively, at baseline, within 2 weeks after EA program completion, and 3 months (± 4 weeks) after EA program completion. Each questionnaire will take approximately 5 minutes to complete.

8.1.1 BPI-SF

The BPI-SF is a 9 item self-reporting questionnaire used to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily functioning. The subject is asked to rate their worst pain in the last 24 hours, least pain in the last 24 hours, average pain intensity, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life. Pain and interference are rated on a 10-point scale (0 = no pain/interference and 10 = pain as bad as you can imagine/complete interference).

8.1.2 FACT/GOG-NTX SUBSCALE

The FACT/GOG-NTX subscale evaluates the subject’s physical, social/family, emotional, and functional well-being. Items are scored on a scale ranging from 0 (not at all) to 4 (very much).

8.2 BLOOD COLLECTION FOR INFLAMMATORY MARKERS

9.0 SERUM SAMPLES FOR ASSESSMENT OF INFLAMMATORY MARKERS, INCLUDING ESR, CRP, TNF-A, IL-1, AND IL-6 WILL BE OBTAINED AT BASELINE AND WITHIN 2 WEEKS AFTER EA PROGRAM COMPLETION. AT EACH TIME POINT, THREE 10-ML TUBES OF BLOOD WILL BE COLLECTED FROM EACH SUBJECT. AE MONITORING

9.1 DEFINITION OF AE

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related.

9.2 DEFINITION OF SERIOUS ADVERSE EVENT

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 CLASSIFICATION OF AN AE

9.3.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system (NCI CTCAE v3.0), the following guidelines will be used to describe AE severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

9.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to the study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and her/his clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study intervention must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

9.3.3 EXPECTEDNESS

The investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All AEs including local and systemic reactions not meeting the criteria for serious AEs (SAEs) will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator or designee will record all reportable events with start dates occurring from informed consent signing until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.5 AE REPORTING

From the time of informed consent signing through 7 days following cessation of the study intervention, all AEs must be reported by the investigator or designee. AEs will be recorded at each examination on the Adverse Event CRFs. AEs should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the subject's CRF. The investigator will make every attempt to follow all subjects with non-SAEs for outcome.

The occurrence of AEs should be sought by non-directive questioning of the subject at each study visit. AEs may also be detected when they are volunteered by the subject during or between visits As far as possible, each AE should be evaluated to determine:

1. Severity grade (CTCAE Grade 1–4)
2. Duration (start and end dates or if continuing at the safety follow-up visit)
3. Relationship to the study intervention (reasonable possibility that AE is related: no, yes)
4. Action taken with respect to the study intervention (none, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious

All AEs should be treated appropriately. Such treatment may include changes in the study intervention including possible interruption or discontinuation, starting or stopping concomitant treatments, hospitalization, or any other medically required intervention. Once an AE is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study intervention, the interventions required to treat it, and the outcome.

9.6 SAE REPORTING

From the time of informed consent form signing through 30 days following cessation of treatment, any SAE or follow-up to a SAE whether or not related to the study intervention must be reported within 24 hours to the Sponsor (CTOMgmt@houstonmethodist.org).

Additionally, any SAE considered by an investigator who is a qualified physician to be related to the study intervention that is brought to the attention of the investigator from the time of informed consent signing through the end of the specified safety follow-up period specified in the paragraph above or at any time outside of the time period specified in the previous paragraph must also be reported immediately to the Sponsor.

All subjects with SAEs must be followed up for outcome.

9.7 REPORTING OF PREGNANCY

Although pregnancy is not considered an AE, it is the responsibility of the investigator or her/his designee to report any pregnancy in a subject (spontaneously reported to them) that occurs during the study.

Pregnancies that occur from the time of informed consent signing through 30 days following cessation of the study intervention must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events. If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor (hmccsaereports@houstonmethodist.org).

10.0STATISTICAL CONSIDERATIONS

Feasibility. The primary objective of this study is to determine the feasibility of a 10-treatment EA program in subjects with CIPN. Based on previous trial results, we can reasonably expect ≥75% of subjects to complete 80% of the treatments. Thus, feasibility will be defined as ≥15 subjects completing ≥8 EA treatments. The proportion of subjects completing ≥8 treatments will

be estimated and a 95% Wilson score confidence interval (CI) will be calculated. Fifteen of 20 subjects completing ≥8 treatments will result in a CI range of 54.2% to 89.0%.

CIPN pain and quality of life. The effect of EA on neuropathic pain control will be analyzed by comparing the worst BPI-SF pain score at baseline with that at each of the post-EA time points (within 2 weeks and 3 months after EA program completion) using a one-sided paired t-test. The paired t-test assumption of normality will be assessed objectively using a Shapiro-Wilk test and visually using inspection of a normal probability Q-Q plot. If the normality assumption is not valid, a nonparametric rank-based method (e.g., Wilcoxon signed-rank test) will alternatively be used. With 20 subjects, a one-sided paired t-test has 80% power to detect a 0.577 standard deviation unit decrease in pain score at the 0.05 significance level. The effect of EA on quality of life will be similarly analyzed using composite FACT/GOG-NTX subscale scores.

IENF density. The Spearman rank correlation coefficient will be used to assess the monotonic relationship between the changes in IENF density at each location (hand and foot) with the change in the worst BPI-SF pain score. With 20 subjects, a one-sided test has 80.2% power to detect a significant positive monotonic relationship between IENF density and pain score at the 0.05 significance level.

10.1 Data Management

CRFs will be designed and utilized to capture all patient data. Data quality control will be performed regularly by the research coordinator/research nurse to ensure timely, accurate, and complete patient data collection.

11.0 ETHICAL CONSIDERATIONS

Compliance with laws and regulations. This study will be conducted in full conformance with the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki.

Institutional Review Board. The protocol and informed consent form will be submitted to the institutional review board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

Informed Consent. The subject will be asked to read and review the IRB-approved consent form. The investigator will explain the research study to the subject and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subjects may withdraw consent at any time throughout the course of the study. A copy of the informed consent document

will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Confidentiality. The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique identification number. Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the informed consent form signed by the subject, unless permitted or required by law. Data generated by this study must be available for inspection upon request by the IRB.

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13.0 APPENDICES

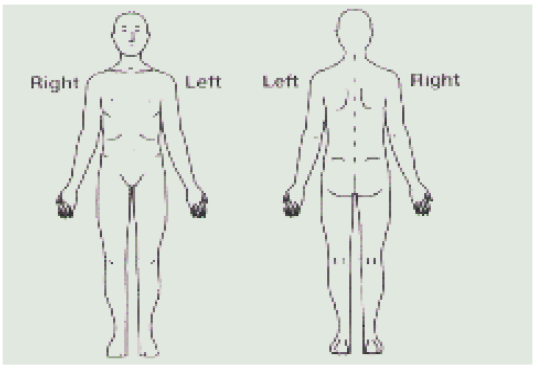
13.1 BPI-SF

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the **average**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain? _____

_____

_____

_____

8. In the last 24 hours, how much relieve have pain treatments or medication provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of Life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

13.2 FACT/GOG-NTX

FACT/GOG-NTX (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

13.3 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

14.0 ABBREVIATIONS

AE	adverse event
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory-Short Form
CI	confidence interval
CIPN	chemotherapy-induced peripheral neuropathy
CRF	case report form
CRP	C-reactive protein
EA	electro-acupuncture
ESR	erythrocyte sedimentation rate
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
IENF	intraepidermal nerve fiber
IL	interleukin
IRB	institutional review board
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PGP9.5	protein gene product 9.5
SAE	serious adverse event
SOA	schedule of activities
TNF-α	tumor necrosis factor-alpha