A double blind randomised controlled study to investigate the effects of Low Level Laser Therapy on Peripheral Neuropathy in Diabetes.

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Diabetic peripheral neuropathy (DPN) is a well know microvascular complication of type 2 diabetes mellitus, it is also observed in type 1 diabetes, and attributed to chronic persistent hyperglycaemia, and is defined as the prescience of peripheral nerve dysfunction in diabetes after the exclusion of other factors (Boulton et al, 1998, Summer et al, 2003, Candrilli et al, 2007, and Herman et al, 2005). DPN, due to lack of sensation to the peripheries, can lead to, infection, ulceration, and thus non-traumatic amputations. Neuropathic pain (NP) has been found to develop in 50% of the individuals suffering from DPN. NP is persistent chronic pain (Bansal et al, 2014).

Studies have spoken about the use of LLLT as a coherent light source for the purposes of pain control, the mechanism of action, by which it relieves pain, still not fully understood. It has been assumed, based on evidence based practice, that any biological effects are secondary to the direct effects of photonic radiation, and are in no way the result of any thermal process (Hagiwara, 2007). Where neuropathic pain is involved, LLLT has been seen to mimic analgesia. Research suggest that LLLT effectively stimulates the local release of neurotransmitters such as serotonin, promoting the release of endorphins, increasing mitochondrial adenosine triphosphate (ATP) production, and through anti-inflammatory effects (Mizutani, 2004).

This study utilised the Erchonia® FX-635™ used in this study is made up of 3 independent 17 mW, 635 nm red laser diodes mounted in scanner devices with flexible arms positioned equidistant from each other and is a variable hertz device.

The variable hertz feature of the Erchonia®FX-635™ is a pulsed wave, defined as containing a selected series of breaks, variances that are preprogramed. This laser utilizes internal mechanics that collects the light emitted from each of the laser diodes and processes each through a proprietary patented lens which redirects the beam with a line refractor. The refracted light is then bent into a spiralling circle pattern that is totally random and independent of the other diodes. Total dosage delivered to the skin during treatment administration is: Intensity x τ(s) = dosage at specific area: 2.46 x 10-3 W/cm2 x (900 seconds) = .0865 J/cm2.

The Erchonia® FX-635™ is classified by the FDA/IEC as a Class 2 laser device. This designation represents a current standard for use to ensure the safety of the subject.

The study subject pollination comprised of male and female adults presenting with an existing clinical diagnosis of diabetes, and with a diagnosed of peripheral neuropathy, and significant spontaneous bilateral foot pain which has been present for the past three months. All patients qualifying for the study were recruited from the principal investigators existing client base or from individuals responded to fliers and advertisements.

In all 30 individuals you were enrolled in the study. Of the 30 participating subjects, 19 were randomised to the active procedure group and 11 were randomised to the placebo procedure group.

All subjects who qualified as eligible for participation in this clinical study satisfy each of the eligibility criteria as outlined in appendix 1

Each subject received twelve (12) total procedure administrations with the Erchonia® FX-635™ (active or sham) across a consecutive six-week period: two procedures per week, each procedure three to four days apart. Exposure time to the Erchonia® FX-635™ was 15 minutes per foot, for a total of 30 minutes per procedure administration. The baseline variables used are were, Duration of foot pain measured in Months/years since their diabetes diagnosis. Insulin dependency, weather the subject was Insulin or non-insulin dependent. Baseline concomitant medication and therapy use were also measured along with standard subject demographics**:** age, gender and ethnicity.

A visual analogue scale was used to measure outcomes. Subjects were asked to rate the overall degree of pain experienced in the feet on a 0-100 mm (0 -10 cm) line. They were instructed to mark this on the scale (line) themselves (a copy of the line and question is in Appendix 2). All subject were instructed to refrain from consuming any pain relief medication within 4 hours of recording a required VAS Degree of Pain.

The NPSI is a 12-item self-administered patient-reported outcome (PRO) assessment tool with a recall/observation period of over the past 24 hours. It contains 10 descriptors representing 5 distinct dimensions based on factor analysis: burning pain, deep pain, paroxysmal pain, evoked pain, paresthesia/dysesthesia, and 2 temporal items designed to assess pain duration and the number of pain paroxysms. The NPSI has been validated in patients with definite neuropathic pain of peripheral or central origin. The total NPSI score is

calculated as the sum of the scores to each individual item, falling within the range of 0 to 100, with higher values indicating greater debilitation due to peripheral neuropathy pain. As this study was conducted in the Republic of Ireland, a rescue pain medication was advised. Subjects were instructed not to record a VAS pain rating (whenever indicated) any sooner than six hours after having consumed a dosage of the study pain relief rescue medication.

Throughout the study duration, subjects were required to maintain a Subject Daily Diary recording the following, as applicable: Rescue Pain Medication Use, Confirmation of Abstinence from Other Pain Medication Use, Other' Non-Pain Relief Medication Use, Adverse Events. As this was a randomised control study, subjects we asked satisfaction questions and if they believed the received the true laser based on their outcomes.

The following time points were used for evaluation across study duration: Baseline (Pre-Procedure), at each of the 12 Procedure Administration visits (following each procedure administration), at each of the 3 Post-Procedure Evaluation visits at 2 weeks, 4 weeks and 3 months' post-procedure.

The following sample demographics were recorded at Baseline evaluation.

Table 1 below shows subject gender breakdown for test and placebo group subjects.

Table 1: Gender by procedure group

Gender	**Test (n=19)**	**Placebo (n=11)**
Male	7	6
Female	12	5

There were slightly more females than males enrolled overall in this study: 17 (57%) females versus 13 (43%) males.

Table 2 below shows the mean and standard deviation in years for test and placebo group subjects.

Table 2: Mean and standard deviation of age by procedure group

Age (years)	**Test (n=18)**	**Placebo (n=11)**
Mean	49.83	53.45
Standard deviation	13.19	11.26

Table 3 below shows ethnicity breakdown for test and placebo group subjects.

Table 3: Subject ethnicity by procedure group

Ethnicity	**Test (n=19)**	**Placebo (n=11)**
Caucasian	13	7
African	2	2
Asian	4	2

Most study subjects overall were Caucasian (67%).

Table 4 below shows the mean and standard deviation of duration of feet pain in months for test and placebo group study subjects.

Table 4: Duration of feet pain by procedure group

Duration of Feet Pain (months)	**Test (n=19)**	**Placebo (n=11)**
Mean	29.47	13.73
Standard deviation	21.06	10.88

Table 5 below shows the time since diagnosis of diabetes in months for test and placebo group subjects.

Table 5: Time since diagnosis of diabetes by procedure group

Time Since Diabetes Diagnosis (months)	**Test (n=19)**	**Placebo (n=11)**
Mean	63.11	40.91
Standard deviation	43.44	26.06

Table 6 below shows the breakdown of test and placebo group subjects who have insulin dependent versus non-insulin dependent diabetes.

Table 6: Insulin dependency by procedure group

Insulin Dependency	**Test (n=19)**	**Placebo (n=11)**
Insulin dependent diabetes	16	7
Non-insulin dependent diabetes	3	4

Most study subjects across both procedure groups had insulin dependent diabetes: 23 subjects (77%)

Table 7 below shows the mean and standard deviation baseline (pre-procedure) VAS feet pain rating for test and placebo group subjects.

Table 7: Baseline feet pain VAS ratings by procedure group

VAS Ratings	**Test (n=19)**	**Placebo (n=11)**
Mean	68.89	65.91
Standard deviation	12.49	10.69

Table 8 below shows the mean and standard deviation baseline (pre-procedure) NPSI total score (0 to 100) for test and placebo group subjects.

Table 8: Baseline NPSI total score by procedure group

NPSI Total Score	**Test (n=19)**	**Placebo (n=11)**
Mean	51.89	53.55
Standard deviation	12.74	16.70

Table 9 below lists the OTC and prescription medications routinely used by test and placebo group subjects at baseline to relieve foot pain.

Table 9: Baseline OTC and prescription medication use for foot pain relief by procedure group

Medication	**Test (n=19)**	**Placebo (n=11)**
Amitriptyline	3	1
Arcoxia	2	-
Lyrica	2	1
Lithium	-	1
Nerve block	-	1
Pain patches	-	1
None	12	6

Table 10 below lists the treatments and therapies routinely used by test and placebo group subjects at baseline to relieve foot pain

Table 10: Baseline treatment and therapy use for foot pain relief by procedure group

Treatment/therapy	**Test (n=19)**	**Placebo (n=11)**
Reflexology	9	3
Physical Therapy & Ultrasound	2	1
Foot massage	1	1
None	7	6

Table 11 below shows the mean, standard deviation and magnitude of the change in feet pain ratings on the VAS from baseline to study endpoint evaluation for test versus placebo group subjects.

Table 11: Baseline and endpoint VAS by procedure group

	Test Group (n=19)		**Placebo Group (n=11)**	
	Mean	**SD**	**Mean**	**SD**
Baseline	68.89	12.49	65.91	10.69
Endpoint	7.92	16.18	56.82	37.99
# *Change*	*-60.97*	*23.28*	*-9.09*	*34.06*

The 60.97-point mean decrease in VAS ratings from study Baseline to Endpoint for test group subjects is almost seven times greater than the relative 9.09-point mean decrease in VAS ratings attained for placebo group subjects.

Chart 1 below shows the mean feet pain VAS ratings across study duration by procedure group.

Chart 1: Mean Feet Pain VAS Ratings Across Study Duration by Procedure Group

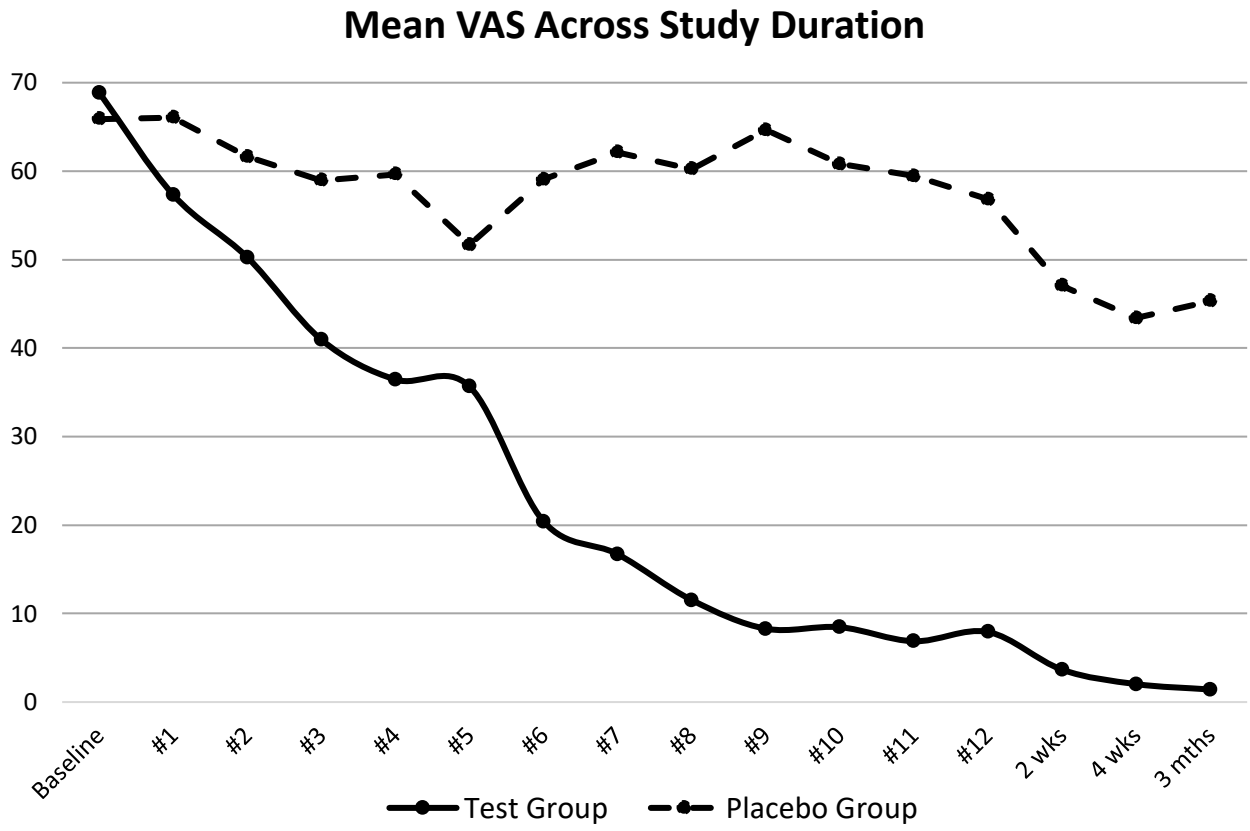


Table 12 below shows the mean and standard deviation total score on the NPSI (range: 0-100) by procedure group across the four evaluation points spanning study duration from baseline to 3 months post-procedure evaluation.

Table 12: Total NPSI score by procedure group across study duration

	Test Group (n=19)		Placebo Group (n=11)	
Total NPSI Score	***Mean***	**St. Dev.**	**Mean**	**St. Dev.**
Baseline	68.89	12.49	65.91	10.69
Procedure Administration #12	57.32	17.89	66.05	10.96
4 Weeks Post-Procedure	2.03	4.73	43.41	27.25
3 months Post-Procedure	1.42	2.31	45.32	28.23

Chart 2 below shows the mean total NPSI score across study duration by procedure group.

Chart 2: Mean Total NPSI Score Across Study Duration by Procedure Group

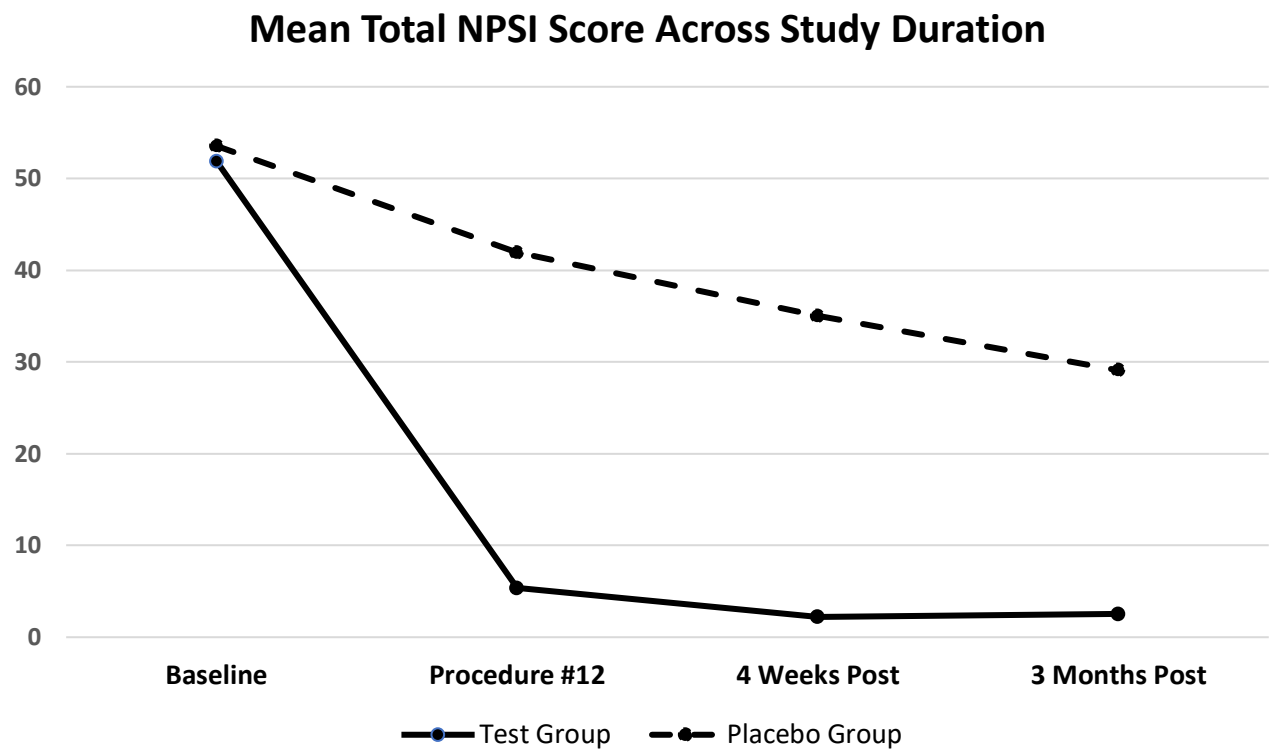


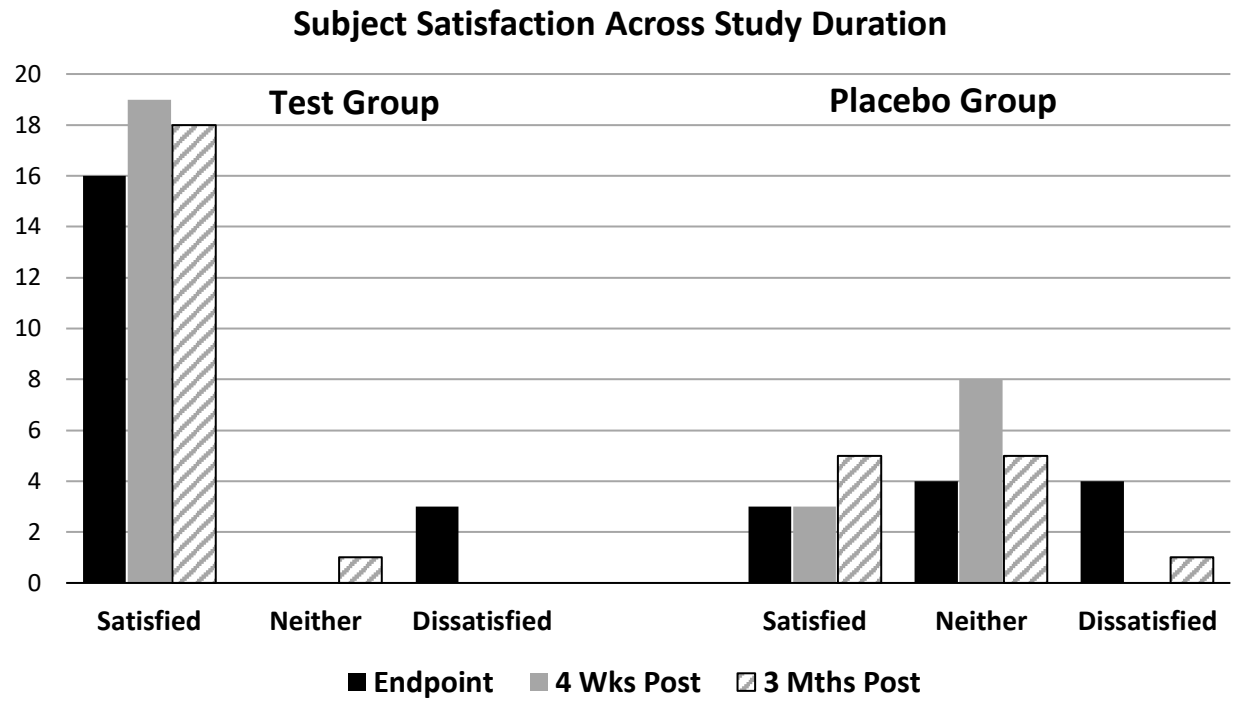
Table 13 below shows the number of subjects who reported each level of satisfaction: 'Satisfied' (Very + Somewhat Satisfied), Neither (Neither Satisfied nor Dissatisfied); and Dissatisfied (Not Very + Not at All satisfied) at each of three evaluation points, by procedure group.

Table 13: Study outcome satisfaction level across study evaluation by procedure group

	Test Group (n=19)			Placebo Group (n=11)		
	Satisfied	**Neither**	**Dissatisfied**	**Satisfied**	**Neither**	**Dissatisfied**
Endpoint	16	-	3	3	4	4
4 Wks Post	19	-	-	3	8	-
3 Mths Post	18	1	-	5	5	1

Chart 3 below shows the number of subjects who were “Satisfied”, “Neither” or “Dissatisfied” with the study outcome across the 3 evaluation points by procedure group.

Chart 3: Subject Study Outcome Satisfaction Across Study Duration by Procedure Group



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Appendix 1

ELIGIBILITY CRITERIA

All subjects who qualified as eligible for participation in this clinical study satisfied each of the following inclusion criteria and none of the following exclusion criteria.

Inclusion Criteria

- Existing clinical diagnosis of diabetes induced Peripheral Neuropathy documented by a suitably qualified and licensed medical professional.
- Significant spontaneous foot pain that occurs approximately equally (comparably) bilaterally.
- Significant spontaneous pain of 50 or greater on the 0-100 VAS for the feet overall.
- Foot pain is chronic, defined as having been ongoing for at least 3 months, bilaterally.
- Subject has been on a stable anti-diabetic medication regimen for the prior 30 days or on no anti-diabetic medication regimen for the prior 30 days.
- Subject is willing and able to refrain from consuming any over-the-counter and/or prescription medication and/or herbal supplements intended for the relief of pain and/or inflammation, including muscle relaxants throughout the course of study participation, except for the study-specific pain relief medication of over-the-counter Tylenol.
- Subject is willing and able to refrain from engaging in any non-study procedure therapies for the management of his or her foot pain throughout the course of study participation, including conventional therapies such as physical therapy, occupational therapy and hot or cold packs, as well as alternative therapies such as chiropractic care and acupuncture.
- Subject agrees to complete the post-procedure phase Subject Diary, as applicable.
- 18 years of age or older.
- Male or female.
- Subject's primary language is English.

Appendix 2

"Using the scale below, please mark with a cross (X) the spot along the 0 to 100 line below that best shows how much **pain you feel in your feet** right now. '0' means you feel no pain at all and '100' means you feel the worst pain imaginable. Please mark only one spot."


no pain
worst pain imaginable
0
100

Exclusion Criteria

- Subject does not have a definitive clinical diagnosis of diabetes induced Peripheral Neuropathy documented by a suitably qualified and licensed medical professional.
- Subject's foot pain is undiagnosed, or has been diagnosed by a qualified medical professional as being other than, or in addition to, diabetes induced Peripheral Neuropathy (such as due to drugs, poisoning, cancer or genetic conditions).
- Subject's foot pain is unilateral or notably different between the two feet (such that the pain in one foot is notably lesser/greater than in the other).
- Subject's self-reported Degree of Pain rating on the VAS pain scale is less than 50 for both feet overall.
- Serious organ disease or other serious primary disease merger.
- Diabetes ketosis, ketoacidosis or severe infection within the past two weeks.
- Current, active chronic pain disease: chronic fatigue syndrome, fibromyalgia, endometriosis, inflammatory bowel disease, interstitial cystitis, peripheral vascular disease.
- Cancer or treatment for cancer in the past 6 months.
- Subject's foot pain is not chronic; that is, it has not been ongoing for at least the prior three months in both feet.
- Use of any one or more of the following <u>analgesics</u>, or an equivalent, <u>within 7 days</u> prior to initiation of the study procedure administration with the Erchonia® FX-635™:
  - ✓ OTC NSAIDs (nonsteroidal anti-inflammatory drugs) such as aspirin, ibuprofen (Advil, Motrin) and naproxen (Aleve),
  - ✓ prescription NSAIDs such as Celebrex, Lodine and Relafen

  N.B.: If any of the above analgesics have been taken within 7 days prior to administration of the initial study procedure, the subject will remain eligible for study participation if he or she agrees to refrain from use of the analgesic(s), and it is medically prudent for him or her to do so, for 7 days prior to initial study procedure administration

- Use of any of the following <u>antidepressants within 30 days</u> prior to initiation of the study procedure administration with the Erchonia® FX-635™ IF consumption of the drug has commenced within that 30-day period:
  - ✓ Tricyclic antidepressants (TCAs) such as Elavil, Pamelor and Norpramin; amitriptyline
  - ✓ Selective serotonin reuptake inhibitors (SSRIs) such as Paxil, paroxetine, fluoxetine (Prozac)
  - ✓ clomipramine (Anafranil)
  - ✓ desipramine (Norpramin)

  N.B.: If the subject has been on a stable dosage any of the above, or any equivalent, antidepressant agent for at least 90 days prior to initial procedure administration, during which time foot pain has been ongoing, then he or she will remain eligible for participation in the clinical study <u>provided that</u> he or she is willing and agrees to maintain that stable dosage throughout the follow-up evaluation phase of the clinical study, and it is medically prudent for him or her to do so.

- Use of any of the following <u>prescription medications within 30 days</u> prior to initiation of the study procedure administration phase:
  - ✓ *Neurontin*
  - ✓ *Lyrica*
  - ✓ *Tramadol*
  - ✓ *Opioid medicines* such as Ultram and Ultracet

  N.B.: If the subject has been on a stable dosage any of the above, or any equivalent, agents for at least 90 days prior to initial procedure administration, during which time foot pain has been ongoing, then he or she will remain eligible for participation in the clinical

study provided that he or she is willing and agrees to maintain that stable dosage throughout the follow-up evaluation phase of the clinical study, and it is medically prudent for him or her to do so.

- Injections of local anesthetics such as lidocaine within the past 30 days.
- Surgical intervention to treat diabetic peripheral neuropathy foot pain, including implantation of a pain relief device.
- Subject is not willing, or is unable, or it is not medically prudent for the subject, to refrain from engaging in any non-study procedure therapies for the management of his or her foot pain throughout study participation, including conventional therapies such as physical therapy, occupational therapy, as well as alternative therapies such as chiropractic care and acupuncture.
- Subject does not agree or is unable to complete the Subject Diary, as applicable, through to his or her study completion.
- Active infection, wound or other external trauma to the areas to be treated with the laser.
- Medical, physical, or other contraindications for, or sensitivity to, light therapy.
- Pregnant, breast feeding, or planning pregnancy prior to the end of study participation.
- Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in past two years.
- Developmental disability or cognitive impairment that in the opinion of the investigator would preclude adequate comprehension of the informed consent form and/or ability to record the necessary study measurements.
- Involvement in litigation and/or receiving disability benefits related in any way to the parameters of the study.
- Subject is less than 18 years of age.
- Participation in a clinical study or other type of research in the past 30 days.
- Subject's primary language is other than English.