2016 Summary
Clinical Trial Results
NCT # 01979367

Lower Extremity Neurological Ischemia
NCT #01979367

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Clinical Trial Policy Site:
Advanced Pain Therapies, LLC
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Dear AASEM Board:

The FDA defines a Pivotal Study as

"…a definitive study in which evidence is gathered to support the safety and effectiveness evaluation of the medical device for its intended use."

Food and Drug Administration Guidance Document: Design Considerations for Pivotal Clinical Investigations for Medical Devices

The AASEM sponsored Physician's Clinical Trial Policy NCT # 01979367 is powered according to the Primary Objective of demonstrating non-inferiority of the devices in question. If non-inferiority is demonstrated via positive responses to the Trial interventions, superiority of the devices and interventions can then be assessed secondarily.

Goal of Trial entails enrolling patients that suffer from multiple painful and debilitating conditions related to the deterioration of the small pain fibers of the lower extremities. Utilizing the Axon II to document the qualitative dysfunction of the A-Delta small pain fibers (spf) as the Objective measure of admittance to the Study, we aim to prove the efficacy of the Study interventions directed at restoring normal function to the A-Delta spf as documented by measurable improvement noted on the Axon II.

Admittance Criteria:

Objective Measures: Axon II sensitivities of spf normally measure **12-30**

Study admittance requires measured sensitivity levels of **>40**

Subjective Measures: Lower extremity neuropathic-type pain complaints

Burning, Stinging, Numbing, nocturnal paresthesias

Edema/Swelling present from mid-tibia distally

Altered Gait/Balance/Proprioception/frequent falling spells

Restless Legs Syndrome

Goals:

Objective Goals: Return Axon II spf measured values to <40 (optimally <30)

Subjective Goals: Reduce subjective pain scores by at least 50%

Reduce edema/swelling by at least 1+ (clinical exam)

Restore normal gait/balance (documented by Heel-Toe capability)

Reduce/eliminate Restless Legs Syndrome (patient report)

Results:

Our Office functioning as a Principal Investigator for 6 months; total of 67 patients enrolled in Study

See enclosed graphs for detailed analysis

- **45/67 (67%) patients had greater than 50% improvement in symptoms**
- **14/67 (21%) of patients had between 1-49% improvement in symptoms**
- **8/67 (12%) of patients had no response**

Brief Discussion

Small sample size limits extrapolation of results, but the **cumulative data-to-date indicates that the Interventions as currently outlined in the Study are beneficial for over 2/3 of the Study Enrollees**.

For a disease entity like Lower Extremity Neurological Ischemia, which currently has no known successful treatment regimen, **the significant lifestyle impact these interventions can have of reducing pain and edema, improving gait capacity, and reducing Restless Legs Syndrome in over 2/3 of study recipients in a high risk patient population aged 65-90 is extremely promising.**

Unanticipated Results:

1. **Restoration of Normal Gait Capacity**
2. **Reduction/Elimination of Restless Legs Syndrome**

Expected results for the Trial Interventions were to reduce pain/swelling in the lower extremities in at least 50% of the patients, and this indeed occurred in over 2/3 of the subjects enrolled in the study.

While the sample size is small, the unexpected overall improvement in normal gait capacity/normal balance (as verified by Heel-Toe Walking) in just over 2/3 of the subjects, and the dramatic reduction of Restless Legs Syndrome in almost all participants both lends credence to the intervention's capabilities as well as potentially expands the overall horizons of the Study.

1. The return to a normal gait in many Study patients after years of imbalance should predictably result in reduced

episodes of falling. This should extrapolate to less hip fractures (and other fractures), in an otherwise very high-risk advanced-age population. **This should have an overall positive impact <u>on both quality and quantity of life</u> in this patient population.** It should also lead to <u>reduced economic outlays</u> by reducing overall need of health care/end-of-life care.

Therefore, moving forward, Heel-Toe walking capabilities, increased ability to perform routine ADL's, and overall patient assessment on increased quality of independent lifestyle possibilities should be added as additional subjective but measurable clinical results of the study.

2. Despite current medical dogma that RLS is <u>a centrally mediated issue</u>, **the study results strongly infer that RLS is causally related to neurological ischemia/small pain fiber nerve damage in the lower extremities (<u>a peripheral neurological ischemia related issue</u>).** Since there is no known cure for this very distressful and disruptive Syndrome, this result is very exciting.

Accordingly, at our Trial Site, we have added patient questionnaires as to the efficacy of the Interventions with specific respect to how the patient feels they have positively (or potentially adversely impacted) their RLS issues. No patient thus far has reported any worsening of the underlying RLS, which is a positive finding in and of itself.

Confounding Variables:

1. **Onychomycosis**
2. **TENS Frequency**

1. **The high prevalence of Onychomycosis in the Study patients is of intriguing significance**. In the small subgroup of patients that responded poorly to the interventions (16/67, or 24%), the vast majority had concurrent fungal infections as evidenced by the presence of Onychomycosis.

Current medical dogma is that podiatric fungal infection is typically irrelevant to the overall health of the patient. Therefore, most practitioners simply disregard this physical finding as inconsequential, perhaps inevitable to the aging process, and elect not to treat the infection.

However, the presence of Onychomycosis in almost all the Trial Study patients strongly implies **a possible causal or resultant relationship of fungal infection and neurological ischemia/ neuropathic pain.** Therefore, we have added the identification of toenail fungal presence/ absence to the physical exam findings both pre- and post-treatment and will accumulate more data in this regard moving forward.

2. The TENS units used at this Trial Site utilize a proprietary frequency modulation encompassing repetitive undulation of stimulation between 4000Hz and 12,000 Hz. The fact that just this year the FDA granted "fast-track" status to an implantable SCS device (*Nevro*) that utilizes similar frequencies (10,000 Hz) with improved success in overall pain control is seemingly validation of combining Anodyne/TENS as utilized in this Trial Study.

According to their marketing literature, these ultra-high frequency devices bring about a physiological modulation of the GABA receptors, thereby reducing overall pain complaints via an "electro-neuro-chemical process." This effectuation is markedly different than a standard SCS implant, which utilizes electrical frequencies at 250Hz to induce paresthesias that essentially counteract ascending chronic pain signals from the lower back and extremities.

It is possible that one of the reasons for the overall success of the Trial Study interventions at this location is related to the simultaneous utilization of <u>both</u> the Anodyne and high-frequency TENS applied in a similar fashion to the high-frequency implantable SCS device. This is intriguing in that relief of lower extremity neurological ischemia/chronic neuropathic pain may very well be accomplished via External Interventions alone.

Since implantable SCS involves many variables and, of course, surgical procedures, there are an entire Pandora 's Box of complications that could possibly be avoided (infections, device failures, patient dissatisfaction, follow-up procedures, etc.) compared to less-invasive but seemingly as efficacious external treatments as demonstrated in this Study.

The inherent usefulness and economic implications of this possibility are themselves tantalizing. **If indeed the patient had the option of externally-applied interventions that could achieve similar global pain reductions without the need for expensive implantable devices, this opens up tremendous possibilities moving forward with alternative treatment options for a subset of neuropathic pain/neurological ischemia patients currently with little to no hope now.**

Conclusions

Obviously, Trial interventions appear to be very beneficial for the targeted patient population. More data is needed to help extrapolate results to broader patient populations. The interesting responses noted with Onychomycosis and Restless Legs Syndrome are worthy of subsequent analysis in follow-up study patients to assess efficacy of Trial interventions with respect to these medical issues as well.

As more data on more Study patients is collected, we can better direct our Objective and Subjective Interventional Measures to help achieve optimal outcomes.

Goals at our Clinical Trial Site moving forward are to triple the number of Study enrollees. We have already had a very positive response by the Patients in the community at-large, and plan to build on this National recognition of the Study results in the coming year.

I would like to thank the AASEM for sponsoring the Study that appears to be so very beneficial for a subset of patients that otherwise have little to no hope of an active, independent, pain-free lifestyle.

I would like to thank the manufacturers of the devices/equipment utilized in the Study:

Axon II/Neuralscan™
Anodyne™ Professional Units
Hakomed™ PRO-ElecDT 2000

Finally, I would like to thank Ron Davis, Brook Davis, and Marlene Eddlemon, and all of the staff at DTSC for handling all

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Respectfully Submitted,
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