

SCIENTIFIC ABSTRACT OF THE CLINICAL PROTOCOL

This is a randomized, double-blind, placebo-controlled, multi-center study to evaluate the therapeutic effect of intramuscular injections of pVGI.1 (VEGF2) as a treatment for patients with thromboangiitis obliterans (TAO) also known as Buerger's disease (BD). The study will randomize up to 40 patients. Patients will be randomized in a 1:1 ratio to receive IM doses of either placebo (vehicle buffer) or a dose of 12 mg (3 x 4mg) of pVGI.1(VEGF2). The investigator may cross patients over to the alternate treatment arm (medication to placebo or placebo to medication) if they have not shown clinically significant improvement following the Primary efficacy end-point evaluation at Week 12.

Initially patients will receive study medication or placebo on three separate treatment days, one treatment day every 2 weeks, over a four to five week period. At each treatment day the study medication will be administered as eight injections into the same general injection area.

At a Week 8 visit Patients will have a safety evaluation and at the Week 12 visit Patients will be evaluated for purposes of the primary efficacy end-point. Following the Week 12 evaluation the Investigator may then progress the patient within the trial along one of the following paths:

- 1) If the week 12 evaluation shows the patient to be improving or have had little improvement of the affected limb then the Investigator may choose to give a second course of three injections to be given over an additional 4 to 5 week period. The study medication used for this series will be the same as was given in the original series of injections.

Regimen	Day 1	Wk 2	Wk 4	Wk8	Wk12	Wk12	Wk 14	Wk16	Wk20	Wk24	Q12Wk	Wk68
Placebo	PBS	PBS	PBS	X	X	PBS	PBS	PBS	X	X	X	X
pDNA	4 mg	4 mg	4 mg	X	X	4 mg	4mg	4mg	X	X	X	X

- 2) If following the Week 12 evaluation the investigator considers the patient to have had little improvement or a clinically significant worsening of the extremity then the Investigator may advise the sponsors medical monitor of this situation and authorization to cross the patient over to a series of doses containing the alternate treatment arm medication for the second three dose series.

Regimen	Day 1	Wk 2	Wk 4	Wk8	Wk12	Wk12	Wk 14	Wk16	Wk20	Wk24	Q12Wk	Wk68
Placebo	PBS	PBS	PBS	X	X	4 mg	4 mg	4 mg	X	X	X	X
pDNA	4 mg	4 mg	4 mg	X	X	PBS	PBS	PBS	X	X	X	X

The second and alternate treatment arm dosing administration schedule and follow-up visit procedures will follow the same schedule as used for the first 12 weeks of the study.

At four and eight weeks following the administration of the last dose of study drug patients will attend Safety evaluation and Second Efficacy End-Point Visits. Following the secondary Efficacy End-Point Visit patients will be required to attend to two additional Safety Evaluation Visits every three months (13 Weeks) until 52 Weeks after the last study medication administration.

The duration of the treatment-periods and Post Treatment follow-up of the patients randomized will be about 28 weeks. The time of patient participation in the study including initial long term follow-up will be up to 1 year following the final injection of study drug. The total time a patient will be asked to attend clinic visits inclusive of initial screening evaluation (signing of informed consent) through the end of long term follow-up may be up to about 75 weeks.

The primary objectives of this study are:

To determine the effect of treatment with pVGL1 (VEGF2) versus placebo, administered intramuscularly into one extremity, on the change score in a composite clinical endpoint from Baseline to Week 12 following the Initial treatment series of study medication.

To evaluate the safety of treatment with pVGL1(VEGF2) versus treatment with placebo, administered intramuscularly into one extremity, by assessing the frequency, duration, and severity of adverse events.

The secondary objectives of this study are:

To determine the effect of treatment with pVGL1 (VEGF2) versus placebo, administered intramuscularly into one extremity, on the duration of exercise ability endpoint (Gardner Treadmill) from Baseline to Week 12 following the Initial treatment series of study medication.

To further explore the effect of continued treatment with pVGL1(VEGF2) or placebo, administered intramuscularly into one extremity, on the change score in a composite clinical endpoint from Baseline (Day 0) and Week 12 and Week 24

To explore the effect of additional treatment with pVGL1(VEGF2) or placebo, administered intramuscularly into one extremity, on changes on a Pain Disability Index in patients with rest pain and claudication from Baseline (Day 0) to Week 12 and at the secondary end point time Eight weeks following the Final Treatment with study medication.

Before any Screening evaluations begin, the patient must sign an IRB approved Informed Consent Document.

This study will consist of:

- 1) Screening Period (up to 6 weeks),
- 2) Baseline Testing (Week -1),
- 3) Treatment Period One (4 weeks),
- 4) Treatment Period One Post-treatment Evaluation at Week 12
[Primary Efficacy Endpoint]
- 5) Second Treatment Period Two (4 weeks optional)
- 6) Treatment Period Two Post-treatment Evaluation at Week 24
[Secondary Efficacy Endpoint], or for selected patients
- 7) "Cross-over" Treatment Period (4 weeks) which will be followed by
- 8) "Cross-over" Post-treatment Evaluation at 8 weeks after last dose.
[Secondary Efficacy Endpoint]
- 9) All patients will, following the last Efficacy End-point, attend additional Post-treatment Safety visits for 52 weeks after the last dose of study medication.

The screening period will begin with patient education and counseling on the contribution of tobacco use to the progression of TAO and patients will be provided with educational materials and suggested behavior modifications as an aid to their quitting the use of tobacco.

After a two week period, patients will attend clinic visits over a maximum of 4 weeks to complete the screening period. The more severely diseased extremity will be selected as the targeted extremity for treatment. For all involved extremities the location of ulcers will be recorded and the areas will be measured. Photographic records will be made of all affected areas. All patients will undergo baseline walking test using the Gardner Protocol, unless in the opinion of the Investigator it is unsafe. Patients will undergo measures of toe pressures in both lower limbs.

At Week -1, each patient will have their condition re-evaluated and an assessment of change in smoking status will be made. Patients with clear Clinical Improvement (resolution of rest pain, visually apparent decrease in

ulcer size, or loss of walking impairment) will not be randomized for treatment. Patients whose condition does not improve or worsens, and that meet all other eligibility criteria, will be randomized for treatment. At Baseline, prior to treatment, the success of tobacco use discontinuation therapy will be evaluated and each patient will be categorized as a tobacco or other nicotine product user or a non-user based on the measurement of cotinine concentrations in a urine or saliva sample obtained at the last pre-study clinic visit. Final Baseline assessments must be conducted on all eligible patients within Week -1 (7 days) days prior to the initial treatment.

During the First Treatment Period, each patient will receive three treatments with either pVGI.1(VEGF2) or PBS solution placebo administered into the targeted limb at 2-week intervals (Day 1, Week 2 and Week 4.) During the First Post-treatment Period, patients will be scheduled to return to the clinic at Week 8 and Week 12 (eight weeks following last injection) for Safety assessments and Primary Efficacy End-point evaluation.

At Week 12 a change from baseline assessment (wound assessments, toe pressure, questionnaires, treadmill testing) will be made. At the Week 12 visit, if in the opinion of the PI, a Second Treatment Period is indicated then each patient will receive three additional treatments with pVGI.1(VEGF2) or PBS solution placebo administered into the targeted limb at 2-week intervals (Week 12, Week 14 and Week 16). During the Second Post-treatment Period, patients will be scheduled to return to the clinic at Week 20 and Week 24 for safety assessments and Secondary Efficacy End-point evaluation.

If at, or following, the Week 12 Evaluation the Investigator deems that the patient's clinical condition has not improved or worsened then the Investigator may request authorization from the Sponsor to cross the patient over to the alternate treatment medication. When this is authorized the patients who received Placebo as Treatment One will cross-over to Medication and Patients who received Medication will cross-over to receive Placebo. Once authorization for this cross-over has been obtained from the Sponsor the Patients crossed-over will be administered three doses of medication during a 4 to 5 week period and will be followed at 4 weeks and 8 weeks following the last dose of medication received, as though they had entered the study from Day 1. A separate set of Case Report Forms will be provided to accommodate this contingency.

All patients will at Week 24 undergo a change from baseline and change from week 12 assessment. Patients will be scheduled to return for additional post-study follow-up visits to explore the durability of treatment outcomes and to have general medical assessments.

Safety and efficacy analyses will be conducted on all patients who are randomized and who receive at least one injection of study medication or placebo, the intent-to-treat population. Data collected regarding patients who sign informed consent are screened and are not randomized will be tabulated and the reasons for screen failure will be evaluated.