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Vascular Voice

MICHIGAN VASCULAR CENTER

Michigan Vascular Center (MVC) - Mission Statement

MVC exists to improve the quality of life for patients by providing the most comprehensive, innovative and best possible vascular care based on sound principles of treatment.

MVC exists to render that care with compassion, respect and integrity; exercising the best possible thought and judgment for the patient's benefit.

REVIVE: Another Marvelous Step for Mankind?

We at the Michigan Vascular Center are pleased and excited to partner with Aastrom in their REVIVE clinical trial to overcome the terrible consequences of end stage critical limb ischemia (CLI).

For the individual with end-stage CLI, and no options left for limb salvage, the REVIVE clinical trial offers hope not only to salvage a limb but even more importantly, to salvage a way of life. For these people, the loss of a leg becomes a major life changing event. Often elderly, frail and nutritionally depleted from their battle with the debilitating effects of constant rest pain, lack of sleep and loss of appetite, these individuals often lack the strength to rehabilitate and use a prosthesis. For them, an amputation means being relegated to a wheel chair at best and for many, being separated from their loved one and spending their time in a nursing home because of the need for assistance. Indeed, for those with CLI, saving a leg is saving a life, saving a way of living and allowing partners to continue to spend their lives together.

For those of us in the vascular field, our careers are dedicated to limb salvage. Yet there are many times when, in the pursuit of that goal, we run out of options and know we must talk to our patients about an amputation. It is never easy to see the loss of hope in their eyes, knowing the difficult reality they face. With REVIVE, we are all hopeful we have entered a new phase in the battle against this crippler of patients. There was a time when going to the moon seemed an impossible task, yet the marvel of man's first step on that planet is indelibly etched in the mind of anyone who was alive to see it. So too was the thought of conquering CLI; yet, with REVIVE, we have the hope that this trial will bring success to patients with CLI and will allow all of us to experience the same marvel of watching them walk, limb intact, because of REVIVE. That, too, will be a marvelous step for mankind.

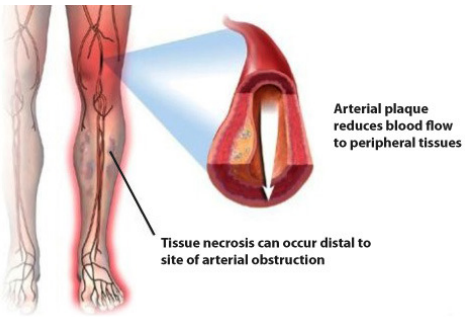
We welcome the opportunity to enroll your patients who qualify for this important clinical trial and thank you for your continued support.

Inside this issue:

Ixmyelocel-T Autologous Multicellular Therapy

Disease State

Critical limb ischemia (CLI) is a serious and life-threatening condition resulting from severe atherosclerotic ischemic disease of the extremities. It represents the most serious manifestation of peripheral arterial disease (PAD) and is characterized by ischemic rest pain or ischemic skin lesions (ulcers or gangrene) (Norgren et al, 2007).



CLI is associated with significant morbidity and mortality: up to 30% of patients will require an amputation within one year and another 25% will die of cardiovascular events (Hirsch et al, 2006; Norgren et al, 2007). The condition occurs in slightly more men than women. Diabetes, abnormal cholesterol levels, chest pain, obesity and increased age are all associated with an increased incidence of CLI.

Treatment of CLI includes risk factor modification, ischemic pain control, management of ischemic ulcers, and revascularization either by open bypass surgery or endovascular approaches (Norgren et al 2007). However, many patients with CLI have multiple co-morbidities which preclude surgery. In addition, patients may have inadequate conduits, complicated/calcified lesions or inadequate outflow tracks which preclude surgical or endovascular interventions (Conte et al, 2009; Schanzer et al, 2010). Major amputation is necessary when there is overwhelming infection that threatens the patient's life, when rest pain cannot be controlled, or when extensive necrosis has destroyed the foot (Norgren et al, 2007).

By definition, no-option CLI patients lack available surgical therapies to prevent amputation and death. There remains a significant need for less invasive therapeutic options in patients with CLI.

Ixmyelocel-T

Ixmyelocel-T is a cellular therapy drug product derived from a patient's own (autologous) bone marrow and contains a mixture of cells, rather than a single cell type. Ixmyelocel-T is composed of a mixed population of cells that include all the major cell types found in bone marrow mononuclear cells (BMMNC). These include myeloid cells (i.e., granulocytes, monocytes, and mixed myeloid progenitors) and lymphoid cells (i.e., T-cells, B-cells, and mixed lymphoid progenitors) that express $CD45^+$ on the cell surface and $CD90^+$ mesenchymal stem/stromal cells (MSCs), and $CD45^+CD14^+$autofluorescent$^+$ ($CD14^+Auto^+$) macrophages. While the cell types are similar to those found in BMMNC, the numbers of $CD90^+$ and $CD14^+Auto^+$ cells are greater in ixmyelocel-T due to expansion during the manufacturing process.

Aastrom Manufacturing System

Ixmyelocel-T is manufactured from a sample (~60 mL) of autologous bone marrow aseptically withdrawn from the posterior iliac crest of a patient under conscious sedation. The bone marrow aspirate sample is shipped overnight to Aastrom's manufacturing facility in an insulated shipping container qualified and supplied by Aastrom.

The ixmyelocel-T manufacturing process is initiated by using an automated, closed system (Sepax Cell Separation System) to perform a Ficoll-based density gradient centrifugation process to deplete RBCs and collect the BMMNCs. The BMMNCs are transferred into a single-use, sterile, disposable cell cassette that is a component of Aastrom's proprietary, automated, closed cell culturing system. Primary components of the cell cassette include a medium reservoir, a bioreactor where the cells are cultured, a waste container, and an electronic application key that directs system processing. Components of the manufacturing system are pictured below.


Single-use Cell Cassette


Automated Instrument Platform

About the Study

The REVIVE trial is a randomized, double-blind, placebo-controlled trial that includes only CLI patients with existing tissue loss who have no other therapeutic or surgical options. The primary objective of the trial will be to assess the efficacy of ixmyelocel-T compared to placebo (vehicle control) on amputation free survival (AFS) at 12 months post-injection in CLI patients with no options for revascularization. Amputation free survival is defined as time to the first occurrence of either major amputation (above the talus) in the index leg or all-cause mortality (death).

An Investigator kick-off meeting was held in December 2011. Eighty sites within the United States will be participating in this clinical trial. See map below for current site locations. Patient screening has begun as of mid-February, 2012.

Basic Inclusion Criteria

- Males and nonpregnant, nonlactating females ages 35 to 90 years of age
- Diagnosis of CLI with tissue loss (corresponding to Rutherford Category 5) having an ulcer size of at least 0.5 cm^2, a smaller sized ulcer penetrating into the subcutaneous tissue, and/or gangrene (dry). In addition, the subject must have ONE of the following documented at screening:
  - Ankle systolic pressure < 70 mm Hg
  - Toe systolic pressure < 50 mm Hg
  - TcPO2 < 30 mm Hg (in a supine position)
- Subjects must have no reasonable standard-of-care options for surgical or endovascular revascularization interventions.
- Subjects must have the following:
  - A narrative documenting the reasons why the site vascular specialist considers the subject "no option". A vascular specialist will be the principal investigator (PI) or subinvestigator and is defined as: vascular surgeon, interventional cardiologist, certified vascular medicine specialist, or interventional radiologist; AND
  - Secondary confirmation by an independent Eligibility Review Committee after review of appropriate documents including, but not limited to: imaging results, medical records, surgical history, site vascular specialist narrative documenting reasons for "no option," and/or lab reports.
- Major amputation in the index leg or death is not anticipated within 3 months of screening in the opinion of the vascular specialist (who must be the PI or subinvestigator)

More detailed information is available at www.revivecli.com or www.clinicaltrials.gov (reference trial identifier NCT01483898).

About Aastrom Biosciences, Inc.

Founded in 1989 and with headquarters in Ann Arbor, Michigan, Aastrom Biosciences is dedicated to the development of treatments for critical cardiovascular diseases. Aastrom is currently evaluating its autologous cellular therapies in late-stage U.S. clinical trials in the treatment of critical limb ischemia and dilated cardiomyopathy (DCM). These critical diseases are associated with significant morbidity and mortality and very limited treatment options.

To fulfill Aastrom's mission of helping people with CLI and DCM realize the promise of patient-specific therapy, we hold fast to our values, always using rigorous scientific methods to test hypotheses and evaluate our products' potential. Personal integrity and accountability to our stakeholders are the foundations of our work, and we seek to practice transparency and openness in our dealings with each other, our patients, and our investors.

Thank You

Aastrom Biosciences, Inc. would like to thank Michigan Vascular Center for allowing them to reach its newsletter readers and let them know about the REVIVE Phase 3 study. As a Michigan company, Aastrom welcomes the opportunity to reach Michigan patients through the study program. Michigan Vascular Center is an experienced clinical site currently participating, and actively enrolling, in the REVIVE Phase 3 clinical trial.

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Michigan Vascular Center
Serving the Community since 1963

MVC Core Values

- We are a professional organization –a team– working equally in a common cause: To provide the best possible vascular care for the physicians, patients, and institutions of our community.
- We share a commitment to excellence in the vascular care of patients through the pursuit of knowledge, communication, innovation, and research.
- We value our employees and incorporate them into our team.
- We commit to each other to honor & pursue these values.

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