# Final Study Summary Report

## An open-label single arm phase 2 proof of concept study to assess the efficacy and safety of ASCT01 in Patients with Critical Limb Ischemia

IND 15069

Summary for end of phase 2 meeting package

August 4, 2017

## TABLE OF CONTENTS

# INTRODUCTION

## Indication/Objectives

### Definition of indication

Critical limb ischemia is a condition in which the blood circulation to the extremities (mostly the legs) is decreased to a degree that pain and non-healing wounds ensue. Mostly, this is a consequence of arteriosclerosis and/or diabetes. If surgical and other methods for improvement of revascularization have failed or are not possible, as a final option these patients need limb amputation.

The Rutherford classification is a standard clinical staging system for peripheral artery disease. The classification has 7 stages;

- Stage 0 – Asymptomatic
- Stage 1 – Mild claudication
- Stage 2 – Moderate claudication
- Stage 3 – Severe claudication
- Stage 4 – Continuous pain
- Stage 5 – Ischemic ulceration not exceeding the digits of the foot
- Stage 6 – Severe ischemic ulcers or frank gangrene

An upward shift of 1 stage indicates improvement, except for stage 5 and 6, where a shift towards stage 3 is required for improvement/

The trial was originally intended to a randomized placebo control but was converted to be performed as an open label single arm clinical trial with ASCT01 administration with approval from FDA. All patients received the autologous ASCT01 treatment. A staggered product administration approach for enrolment was used -a minimum of one week between administrations of the product to the first five subjects was allowed to study any potential effects of the product and/or the administration process.

The treatment- was a one-time, one dose application carried out by the treating physician - via angiographic application (80% of the dose). The remaining 20% ASCT01 was injected intramuscular distal of the obstruction and along the anatomic course of the artery or the neurovascular bundle in the ischemic limb. Selection and follow-up evaluation was performed by the investigators at the site.
This Phase II (proof of concept) trial was conducted as a clinical study. A total of 33 male and/or female patients were screened, and 24 evaluable patients, completed the study. The patients were evaluated till one year (12 months) post-administration with last patient out on March 30, 2017.

Other variables also effect outcomes and reported mortality in success of revascularization, which also correlates with the severity of the disease at presentation. Rutherford stage 4 patients generally appear

to do better than stage 5; specifically, those requiring early major amputation. The stage 5 group generally is expected to have aggressive atherosclerosis, and rapid progression happens. This may occur with intra-plaque hemorrhage, or just proliferation. Patients may progressive because of proximal disease changes as seen on a few MRA's. Resumption of smoking also appears to have a clear negative effect.

The primary efficacy outcome is considered a success if at 3 months after administration of the cell treatment there is no major amputation or has shown a 15% increase in ankle-brachial index (ABI) or transcutaneous oximetry measurement (TCOM) from the measured baseline data**.** Other secondary variables such as pain analysis, would healing, angiography and walking distance, were also evaluated in this study for investigative purpose. The following summary is a review of the outcomes.

## SUMMARY OF PRIMARY EFFICACY RESULTS:

**Major Amputations:** There were 2 major amputations (both below knee) during the 3-month period (**Table 5**). Both major amputations occurred in patients who were Rutherford 5 at screening. Among patients who were Rutherford 5 at baseline, major below amputations occurred in 8% of the patients during the 3-month period. 2 more major amputation occurred during the 6-month period evaluation and an additional 2 amputations occurred between the 6-month and the 12-month monitoring period or a total of 6 major amputations, however one of these patients received an amputation at a different clinic within 33 days of the treatment. There were minor toe amputations recorded for 2 patients after the 3-month period. Major amputation rates of 30 to 40% are not uncommon in such patients and has been seen in other studies. Rutherford 5s enrolled with insufficient time for the stem cell effect may also exhibit rapid progression of other disease potentially leading to amputation. The late amputation patients who underwent below knee amputations have shown improvement after the cell therapy and in some cases preventing an above knee amputation.

### ABI and TcPO2

The ankle-brachial index is an efficient tool for objectively documenting the presence of lower-extremity peripheral arterial disease (PAD) and critical limb ischemia (CLI). It is a simple, reproducible, and cost-effective assessment that can be used to detect lower-extremity arterial stenosis in the primary care setting and transcutaneous oxygen measurement (TCOM or $TcPO_2$) is a non-invasive method of measuring the oxygen level of the tissue below the skin. Since oxygen is carried by the blood, TCOM can be used as an indirect measure of blood flow to the tissue. Since blood flow is important for wound healing, TCOM is often used to gauge the ability of tissue to effectively heal. These parameters are used as combined primary parameters in the study.

There was more than 15% improvement in ABI and/TcPO2 measurements in 12 patients from that obtained at treatment date and in the open-label phase of the trial at 3 months with some showing additional improvements at 6 months. One patient showed a 14.89% more increase (**Table 2**).

## SUMMARY OF MAJOR SECONDARY EFFICACY RESULTS:

### Pain Analysis

Pain was assessed using a 10-point VAS scale. No absolute change on the VAS scale from baseline was required to denote either improvement or worsening, the intent was to evaluate change only from baseline. 13 patients showed a significant reduction of pain in the compared to the pain scale at treatment and 3- month endpoint and 14 at 6-month visit. The pain analysis was however inconclusive since most of the study patients were also under standard analgesic treatment.

### Walking distance

Walking distance by walking distance measurements at baseline and various visits during the study was evaluated. However, due to pain or associated comorbidities, many did not complete or even attempt the test. Some improvement was observed in a number of patients from baseline vs various visits.

### Quality of life

Quality of life was measured using the EQ-5D questionnaire at baseline and 3 months and continued at all visits. Some patients demonstrated improvements compared baseline.

### Ulcer and Wound Healing

Wound size, wound healing stages according to the Wagner classification were reviewed. At 3 months significant changes were not observed, longer period and repeat therapy maybe required for healing progression of ulcers. Rutherford scale changes in some patients is indicative of potential healing was observed however. consistency could not be observed in this patent group.

## SUMMARY OF SAFETY EVALUATION:

### Safety and adverse events

There was one death 6 months after treatment however the coroner's information and PIs statement have conclusively ruled out any causative link to the stem cell treatment. There were no severe unexpected adverse events during this 3-month reporting period and later (Table 4 (a, b and c)). Bone marrow aspiration was well tolerated with no complications in most and only minor complications in some related to injection pricks. The hematology values have not shown any trends. Muscle injury due to the intramuscular injections was not observed clinically or any adverse effects or embolism with the infusion process were noted. Ophthalmologic examinations at screening demonstrated baseline proliferative

retinopathy in some patients, but there were no cases of worsened or new retinopathy. There were no clinically evident cases of new or recurrent malignancy. No significant cardiovascular adverse events were observed.

## SUMMARY OF STUDY

## 1. SUMMARY PAGE

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| **Study title** | An open-label single arm phase 2 study to assess the efficacy and safety of ASCT01 in Patients with Critical Limb Ischemia. |
| **Treatment** | About 200 mL (150 +/- 50 mL) of the patient's bone marrow (BM) is aspirated from the ileac crest (s). The bone marrow was then transported to a processing site and processed to produce ASCT01 by a qualified institution operating under FDA cGMPs and cGTCPs.<br><br>In the current study al patients, BM harvest, processing and treatment steps were completed on the same day, however the stability profile of ASCT01 allows for treatment within three days (72 hrs) after the bone marrow harvest.<br><br>After angiographic visualization of the arterial stenosis in the affected limb, 80% of ASCT01 was infused intra-arterially proximal to the stenosis. The remaining 20% ASCT01 was injected intramuscular (IM) distal to the obstruction along the anatomic course of the artery and the neuro-vascular bundle in the ischemic limb (at least 6 injections). The infusion dose was approximately 10 million cells per mL infused at a rate of 5 ml per minute using suitable catheters qualified for the administration. The sequence of the IM and IA administration was at the investigators discretion. The intra-arterial infusion occurred via a metered infusion system (BBraun Syringe pump or similar) that accommodating a 50-60 ml syringe and infuse rates capability of 0-999ml/hr) with either a Quick Cross Catheter of 0.035" (catalog 518-038) or 0.018" (catalog 518-035) ID.<br><br>The ASCT01 (cellular composition) prepared by minimal manipulation is administered as entirely prepared from the bone marrow, cell count and viability varies with individual characteristics. The agency has reviewed the ASCT01 process and has confirmed that this process can be characterized as minimally manipulated - Appendix 1. |

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| **Indication studied** | Patients with established CLI (confirmed by Rutherford Stages 4 to 5) with angiographic evidence of significant infra-inguinal arterial occlusive disease. |
| **Study design** | An open-label single arm phase 2 interventional single arm proof of concept study to assess the efficacy and safety of ASCT01 in Patients with Critical Limb Ischemia (CLI) who would otherwise need amputation. For this trial, patients with a severe grade of CLI and categorized in the group of failed traditional revascularization treatment patients (no option patients) were enrolled. |
| **Trial Objective** | At 3 months, a combined primary endpoint of major amputation (above the ankle) or persisting critical limb ischemia (no clinical or perfusion improvement) will be evaluated by comparison of treatment group with baseline data. |
| **Primary Outcome measures** | The primary outcome variable is "**treatment failure**" defined as major amputation (above the ankle) of the affected limb within 3 months or an unchanged critical limb ischemia of the affected limb after 3 months defined as less than 15% change in $tcPO_2$ or ABI or absolute ankle pressure. |
| **Sponsor** | **Lifecells, LLC.**<br>68 Discovery<br>Irvine, CA 92618<br>USA |
| **Study Protocol No.** | IND 15609 (Approved on December 13, 2012) |
| **Development phase of study** | Phase 2a (Proof of Concept) |
| **Number of Patients** | • No. of subjects planned: 24<br>• No. of subjects screened: 38<br>• No. of subjects treated: 24<br>• No. of subjects withdrawn: 01 (KCV2-016 voluntary after 6 months)<br>• No. of subjects dropped out: 02 (KCV2-004 non-complaint)<br>• KCV2-006 deceased due to unrelated issue after completion of 6 months<br>• No. of subjects completed the study: 24<br>• No. of subjects analyzed for efficacy statistical analysis: 24 |

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| **Number of Study Sites** | One (Kansas City Vascular Foundation, now Midwest Aortic and Vein Institute ( MAVI)), |
| **First Patient in Date:** | 2 February 2014 (Informed consent date) Dose Date: 02/20/2014 |
| **Last Patient Dosed** | 30 March 2016 |
| **Last Patient Primary end point date (3 mos)** | 3 June 2016 |
| **Last Patient Out (scheduled)** | 30 March 2017 (safety parameter only- Visit 7) |
| **Principal Investigator** | **Dr. Karl Stark, MD**<br>Principal Investigator<br>Kansas City Vascular Foundation<br>2750 Clay Edwards Drive Suite 310<br>City, State, Zip: North Kansas City, MO 64116<br>Email: kstark@mavi.com<br>Phone 816-842-5555 |
| **Sponsor's Representative** | Paul T Sudhakar<br>President and CEO<br>Lifecells LLC.<br>68 Discovery<br>Irvine, CA 92618<br>Telephone: (816) 507-8249<br>Email: pauls@ptspharma.com |
| **Date of study report** | July 29, 2017 |
| **This study was performed per the current protocol at the time of dosing and IRB approval and in compliance with Good Clinical Practices (GCP) and Good Laboratory Practices (GLP)** | |

## 2. SYNOPSIS

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| **Name of Sponsor / Company:** Lifecells LLC., USA | | |
| **Name of Finished Product:** ASCT01 (Autologous Stem Cell Transplantation) | | |
| **Treatment:** ASCT01 (autologous stem cell transplantation) | | |
| **Title of Study** | An open-label single arm phase 2study to assess the efficacy and safety of ASCT01 of Lifecells LLC, in Patients with Critical Limb Ischemia. | |
| **Investigators** | **Dr. Karl Stark, MD**<br>Principal Investigator<br>Kansas City Vascular Foundation<br>2750 Clay Edwards Drive Suite 310<br>City, State, Zip: North Kansas City, MO 64116<br>Email: kstark@mavi.com<br>Phone 816-842-5555<br>Scott W. Kujath, MD<br>Kansas City Vascular Foundation<br>Email: skujath@mavi.com<br>Phone 816-842-5555<br>Role: Co-PI<br>**Clinical Research Coordinator:**<br>Rebecca Thomas, ANP-BC<br>Kansas City Vascular Foundation<br>Email: rthomas@mavi.com<br>Phone 816-842-5555<br>**Statistician**:<br>Alex Dmitrienko, PhD<br>Principal biostatistician<br>Mediana, Inc | |

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| **Study Center** | Kansas City Vascular Foundation<br>2750 Clay Edwards Drive Suite 310<br>City, State, Zip: North Kansas City, MO 64116<br>Email: kstark@mavi.com<br>Phone 816-842-5555 |
| **Publication (reference)** | None at This - To come later |
| **Statistical Facility** | Mediana, Inc |
| **Study start date** | 2 February 2014 |
| **Study end date** | 30 March 2017 |
| **Phase of development** | Phase 2a (Proof of Concept) |
| **Objectives** | **Primary Objective:**<br>At 3 months, a combined primary endpoint of major amputation (above the ankle) or persisting critical limb ischemia (no clinical or perfusion improvement) was evaluated by comparison of treatment group with baseline data.<br>**Secondary Objectives**<br>After 3 months:<br>- Time to treatment failure<br>- Time to amputation<br>- Changes in transcutaneous oxygen pressure (TcPO2)<br>- Changes in ankle-brachial pressure index (ABI)/toe brachial pressure index (TBI)<br>- Rate of minor amputations in the affected limb (below the ankle)<br>- Wound/Ulcer healing (wound size, wound stage according to the Wagner classification, wound healing stages according to the Reike classification picture)<br>- Pain (visual analog scale)<br>- Analgesics use<br>- Quality of life (EQ-5D Questionnaire, Peripheral Vascular Questionnaire)<br>- Rutherford grade and stage<br>- Collateral arteries as judged by magnetic resonance angiography after 3 months<br>- Measurement maximal walking ability in speed and distance without or with pain<br>- Rate of major adverse cardiovascular events |

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| **Design Methodology** | An open-label single arm phase 2 study to assess the efficacy and safety of ASCT01 in Patients with Critical Limb Ischemia (CLI) who would otherwise need amputation. For this trial, patients with a severe grade of CLI and categorized in the group of failed traditional revascularization treatment patients (no option patients) were enrolled.<br><br>Selected patients received ASCT01 treatment. The patients in the treatment group underwent bone marrow collection for aspiration of about 200 mL of bone marrow from the Ileac crest(s). The bone marrow was processed to the required dilution of the ASCT01 at Kansas University Midwest Stem Cell Research Center and Biomedical Devices of Kansas operating under FDA cGMPs and cGTCPs.<br>The bone marrow collection and the treatment occurred for all patients on the same day. Although there is a provision for treatment up to 72 hrs hold time if required, all the patients in this group were treated with the stem cell product on the same day of the bone marrow harvest.<br><br>After angiographic visualization of the arterial stenosis in the affected limb, about 80% of diluted ASCT01 was infused intra-arterially (IA) proximal to the stenosis. The remaining 20% ASCT01 was injected intramuscularly (IM) distal to the obstruction along the anatomic course of the artery and the neuro-vascular bundle in the ischemic limb (at least 6 injections). The infusion dose is 10 million cells per mL infused at a rate of 5 ml per minute using suitable catheters qualified for the administration. The sequence of the IM and IA administration was at the investigators discretion.<br><br>The intra-arterial infusion occurred via metered infusion system (Braun Syringe pump or similar) that accommodated a 50-60 ml syringe and can infuse at rates of 0-999ml/hr) with either a Quick Cross Catheter of 0.035” (catalog 518-038) or 0.018” (catalog 518-035) ID.<br>After ASCT01 administration, the patients were evaluated at 3 months for the primary end points evaluation and monitoring continued for a total period of 12 months (the visit schedule table is at the end of the synopsis). |

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| | A staggered product administration approach for enrolment was used -a minimum of one week between administrations of the product to the first five subjects for safety check of the administration. |
| **Number of subjects (Table 3 – Demographics)** | • No. of subjects planned: 24<br>• No. of subjects screened: 38<br>• 5 excluded after informed consent<br>• 9 excluded before informed consent<br>• No. of subjects treated: 24<br>• No. of subjects withdrawn: 02 (KCV2-016 Voluntary KCV2-017 BKA)<br>• No. of subjects dropped out: 01 (KCV2-004 non-complaint)<br>• One subject KCV2-006 deceased after 6 mos (determined unrelated to the treatment<br>• No. of subjects completed the study: 24<br>• No. of subjects analyzed for efficacy statistical analysis: 24 |
| **Diagnosis and criteria for inclusion** | 1. Male and Female patients in the age group of 18-80yrs.<br>2. Established CLI (confirmed by Rutherford 4 to 5) with angiographic evidence of significant infra-inguinal arterial occlusive disease<br>3. Ankle Brachial Pressure Index (ABI) ≤ 0.6 or the absolute ankle blood pressure < 60 mm Hg *or* TcPO2<20 mmHg without tissue loss or TcPO2<40 mmHg if there is tissue loss or alternatively toe Brachial Pressure Index (TBI) less 0.5 or the absolute toe blood pressure less than 50 mm Hg<br>4. No surgical or interventional option for revascularization and no response to best standard care delivered as confirmed by a vascular surgeon and/or physician.<br>5. No immediate life-threatening complication from CLI which would demand immediate amputation. |

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| | 6. Patients who are able to understand the requirements of the study, and willing to provide voluntary written informed consent, abide by the study requirements, and agree to return for required follow-up visits.<br>7. On optimal medical therapy<br>8. If diabetic, HgbA1c <10% |
| **Exclusion Criteria** | 1. Acute life threatening complication of limb ischemia with the need for immediate limb amputation to avoid death or clinical deterioration<br>2. Patients with confirmed Rutherford 6 condition with extensive tissue damage<br>3. Patients with documented terminal illness or cancer or any concomitant disease process with a life expectancy of less than 6 months.<br>4. Patients with a history of severe alcohol or drug abuse within 3 months of screening.<br>5. Known bone marrow diseases which preclude transplantation.<br>6. End-stage renal failure on regular dialysis treatment. Creatinine ≥2.0 mg/dl<br>7. Patients already enrolled in another investigational drug trial or completed within 1month.<br>8. Pregnancy.<br>9. Patients tested positive for HIV screen1or2, Hepatitis C Antibody Hepatitis Bsurface-antigen, HepatitisBcore Antibody, Syphilis screen<br>10. Myocardial infarction / CVA / TIA within the past three months prior to enrollment<br>11. Revascularization procedure in target limb within 6 weeks prior to enrollment<br>12. Laboratory values as show below*<br>13. Currently taking immunosuppressive agents<br>14. If diabetic, diagnosis of proliferative retinopathy<br>15. Patients with infected ulcers or systemic infections |

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| | *Laboratory Values:<br>Hemoglobin <10 g/dL<br>Platelet count <100,000/microL<br>ALT >60 U/L<br>AST >60 U/L<br>Bilirubin >1.0 mg/dL<br>INR >1.3 unless on Coumadin and at Investigator discretion<br>APTT >40 second unless on Lovenox or Heparin and at Investigator's discretion |
| **Treatment** | Lifecells Stem Cell Product (ASCT01) diluted to 10 million CD45+ per mL for infusion and injections |
| **Lot No.** | Each patient is treated as a lot number for the ASCT01 (Table 6 - product information). The certificates of release testing and analysis will be provided in module 3 of the IND file for the phase 3 study or as requested by the Agency. |
| **Treatment and mode of administration** | Single treatment only in the proof of concept study administered about 80% of diluted ASCT01 as infusion intra-arterially (IA) proximal to the stenosis. The remaining 20% ASCT01 was injected intramuscularly (IM) distal to the obstruction along the anatomic course of the artery and the neuro-vascular bundle in the ischemic limb (at least 6 injections). The infusion dose is 10 million cells per mL infused at a rate of 5 ml per minute using suitable catheters qualified for the administration. |
| **Duration of the treatment** | A single treatment was administered on same day. Total duration of the study from the check in of period one to the last evaluation was 365 days. |
| **Criteria for evaluation: Safety Evaluation** | - Adverse events<br>- Vital signs<br>- Standard biochemical safety variables |

**Table 1:** Clinical Trial Monitoring Chart**.**

| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|

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| Written informed consent | X | | | | | | |
| Inclusion criteria | X | X | | | | | |
| Exclusion criteria | X | X | | | | | |
| Randomization | | X | | | | | |
| Demographic data | X | X | X | X | X | X | X |
| Medical History-Angiogram CD & Medical Records Required to be provided at this time | X | | | | | | |
| 6 min Walking test | X | | | X | X | X | X |
| Quality of Life& Peripheral Vascular Questionnaires,<br>VAS (Pain Score) | X | | | X | X | X | X |
| Ankle-Brachial Pressure Index (ABI) / Toe Brachial Pressure Index (TBI) | X | | X | X | X | X | X |
| Transcutaneous oxygen pressure (TcPO2) | X | | | X | X | X | X |
| Wound/ulcer examination(Wagner/Reike/Picture) | X | | | X | X | X | X |
| Physical Examination | X | | X | X | X | X | X |
| Rutherford assessment | X | | | X | X | X | X |
| Vital signs | X | X | X | X | X | X | X |
| ECG | X | X | | | | | X |
| Infectious Serology-Screening HIV1-2, Hepatitis C Antibody Hepatitis B surface-antigen, Hepatitis B Core Antibody, Syphilis screen, | X | | | | | | |
| Pregnancy test / Use of contraception | X | | | | | | |
| Blood Labs- Hematology-CBC with Diff, CMP, lipid panel, C-Reactive Protein<br>**At Day 7 only CBC with Diff* | X | | X* | X | X | X | X |
| INR & APTT for patients on anticoagulation therapy | X | X | | | | | |
| HbA1c for DM subject's only | X | | | | X | X | X |

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| Retinal examination (diabetic subjects only) | X | | | | | X | |
| Bone Marrow Collection | | X | | | | | |
| Angiography with contrast | | X | | | | | |
| MR Angiography with contrast | | X | | | X | | |
| Stem cell transplantation: ASCT01 - | | X | | | | | |
| Record Adverse Events/Serious Adverse Events | | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X |
| Record Analgesic(s) Use | X | X | X | X | X | X | X |

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| **Statistical Evaluation** | Statistical analysis was performed using SAS® package (SAS Institute Inc., USA, Version 9.3). for subject size requirement and power of the study based on the outcomes in the proof of concept. Comparative analysis for the number of treatment failures (i.e. major amputations or the number of unchanged Critical Limb Ischemia) for the treatment group with baseline data and the outcomes.<br><br>Other Analyses of time to treatment failure and of time to amputation for the treatment group was evaluated.<br><br>An external Data Safety Monitoring Board (DSMB) was used to oversee the conduct of the study as outlined in the DSMB Charter. The DSMB had access to the data and performed the following functions:<br><br>1. Review the conduct of the study and accruing safety data at interim analysis.<br>2. Review safety data on an ad hoc basis as safety questions arise.<br><br>The DSMB was allowed to stop the study at any point in time, if the safety of the patients is at stake. The decision to stop the study can also be made by the PI, for safety reasons.<br><br>**Members of DSMB**:<br><br>**Chairman:** Charles Ward Van Way III, M.D , Professor of Surgery Sosland / Missouri Endowed Chair of Trauma |

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| | Services, Director, Shock Trauma Research Center, University of Missouri - Kansas City<br>2411 Holmes Street, Kansas City, Missouri, 64108 TEL: (816) 404-5364, (816) 235-2553.<br>EMAIL: vanwayc@umkc.edu<br>Robert Rick Carter, M.D Vascular Surgeon<br>Kansas City Vascular, PC<br>2750 Clay Edwards Drive Suite 304<br>Kansas City MO 64116-3256 TEL: (816) 842-5555<br>FAX: (816) 842-8888<br>EMAIL: rcarter©kcvascular.com<br>Statistical Consult: Nilofer Qureshi, Ph.D Professor, Basic Medical Science, , University of Missouri - Kansas City<br>2411 Holmes Street, Kansas City, Missouri, 64108 TEL: 816-587-3642, office; 816-235-1056, Cell: 816-721-2281<br>EMAIL: qureshin@umkc.edu<br>Specific statistical measures and methods (per FDA guidance, regulations and scientifically accepted methods) |

**Table 2**: Efficacy Outcome Based on Primary Endpoints at 90 days (visit 5) Evaluation

| Primary Endpoint | Subject Identifier for the Study KCV2-00 | ABI at Visit 1 | ABI at Visit 5 | TcPO2 at Visit 1 | TcPO2 at Visit 5 | Amputation | Percent Change in ABI at Visit 5 | Percent Change in TcPO2 at Visit 5 | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Failure | 1 | 0.74 | 0.64 | 29 | 14 | | -13.51 | -51.72 | Failure % change is less than 15% for both ABI and TcPO2 |
| Failure | 2 | 0.01 | 0.44 | 5 | | Major | 4300 | | Failure due to major amputation |

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|---|---|---|---|---|---|---|---|---|---|
| Failure | 3 | 0.01 | 0.01 | 7 | 5 | | 0 | -28.57 | Failure % change is less than 15% for both ABI and TcPO2 |
| Failure | 4 | 0.23 | | 10 | | Major | | | Failure due to major amputation |
| Success | 5 | 0.46 | 0.73 | 39 | 28 | | 58.7 | -28.21 | |
| Success | 6 | 0.38 | 0.52 | 2 | 27 | | 36.84 | 1250 | |
| Success | 7 | 0.49 | 0.58 | 40 | 35 | | 18.37 | -12.5 | |
| Success | 8 | 0.58 | 0.83 | 3 | 39 | | 43.1 | 1200 | |
| Success | 9 | 0.47 | 0.58 | 41 | 60 | | 23.4 | 46.34 | |
| Failure | 10 | | | 53 | 51 | | | -3.77 | Failure % change is less than 15% for TcPO2 |
| Success | 11 | 0.49 | 0.57 | 15 | 47 | | 16.33 | 213.33 | |
| Failure | 12 | 0.55 | 0.57 | 60 | 28 | | 3.64 | -53.33 | Failure % change is less than 15% for both ABI and TcPO2 |
| Failure | 13 | 0.5 | 0.56 | 19 | 20 | | 12 | 5.26 | Failure % is less than 15% for both ABI and TcPO2 |
| Failure | 14 | 0.54 | 0.46 | 66 | 49 | | -14.81 | -25.76 | Failure %is less than 15% for both ABI and TcPO2 |
| Success | 15 | 0.21 | 0.51 | 2 | 20 | | 142.86 | 900 | |
| Failure | 16 | 0.24 | 0.18 | 19 | 2 | | -25 | -89.47 | Failure % change is less than 15% for both ABI and TcPO2 |
| Success | 17 | 0.48 | 0.3 | 2 | 3 | | -37.5 | 50 | |
| Failure | 18 | 0.46 | 0.25 | 44 | 33 | | -45.65 | -25 | Failure % is less than 15% for both ABI and TcPO2 |
| Failure | 19 | | | 32 | 13 | | | -59.38 | Failure % change is less than 15% for TcPO2 |
| Success | 20 | 0.17 | 0.31 | 16 | 11 | | 82.35 | -31.25 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Success | 21 | 0.19 | 0.34 | 11 | 26 | | 78.95 | 136.36 | |
| Success | 23 | 0.4 | 0.48 | 41 | 41 | | 20 | 0 | |
| Failure | 24 | 0.43 | 0.43 | 47 | 54 | | 0 | 14.89 | Failure % change is less than 15% for both ABI and TcPO2<br>(nearly a 15% TcP02 increase) |
| Success | 25 | 0.3 | 0.36 | 17 | 42 | | 20 | 147.06 | |

*KCV2-002 – BKA 4/22/14

*KCV2-004 - Had amputation from another doctor outside the study within the 30 days after the stem cell transplantation (non-complaint)

*KCV2-010 - ABI could not be measured occluded.

*KCV2-017- non-complaint withdrew from study

*KCV2-019 - ABI is of Toe (not taken into consideration will pass with TCOM)

**Success Rate: All 24 patients = 50%**

**Table 3**: Demographic Data of All Patients Treated

| Patient ID | Sex | Age (Years) | Race | Height (cm) | Weight (Kg) | Treatment Limb | Smoking Status | Remarks |
|---|---|---|---|---|---|---|---|---|
| KCV2-001 | Male | 81 | Caucasian | 180 | 65.4 | Left | Former | Diabetic |
| KCV2-002 | Male | 54 | Caucasian | 170.2 | 93 | Left | Current | Diabetic |
| KCV2-003 | Male | 50 | Caucasian | 172.7 | 104.3 | Left | Former | Non-diabetic |
| KCV2-004 | Female | 59 | Caucasian | 160 | 49.9 | Left | Current | Non-diabetic |
| KCV2-005 | Female | 62 | Caucasian | 162.56 | 90.9 | Left | Former | Diabetic |
| KCV2-006 | Male | 50 | Caucasian | 180.3 | 170 | Right | Former | Non-diabetic |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| KCV2-007 | Male | 60 | Caucasian | 175.3 | 106.3 | Right | Current | Non-diabetic |
| KCV2-008 | Male | 75 | Caucasian | 172.7 | 60.5 | Left | Former | Non-diabetic |
| KCV2-009 | Female | 43 | Caucasian | 154.9 | 103.6 | Left | Former | Non-diabetic |
| KCV2-010 | Male | 77 | Caucasian | 177.8 | 79.5 | Right | Former | Diabetic |
| KCV2-011 | Female | 80 | Caucasian | 152.4 | 62.2 | Left | Never | Diabetic |
| KCV2-012 | Male | 62 | Caucasian | 175.3 | 83.6 | Left | Former | Diabetic |
| KCV2-013 | Male | 74 | Hispanic | 167.6 | 56.4 | Right | Former | Diabetic |
| KCV2-014 | Male | 59 | Caucasian | 172.7 | 65.8 | Left | Current | Non-diabetic |
| KCV2-015 | Male | 78 | Caucasian | 175.3 | 65.9 | Left | Former | Non-diabetic |
| KCV2-016 | Male | 67 | Caucasian | 187 | 86 | Right | Current | Non-diabetic |
| KCV2-017 | Male | 72 | Caucasian | 165.1 | 65.9 | Left | Current | Non-diabetic |
| KCV2-018 | Male | 82 | Caucasian | 190.5 | 89.5 | Left | Former | Non-diabetic |
| KCV2-019 | Male | 82 | Caucasian | 172.7 | 76.1 | Left | Former | Non-diabetic |
| KCV2-020 | Male | 68 | African American | 187.9 | 118.3 | Left | Former | Diabetic |
| KCV2-021 | Female | 66 | Caucasian | 167.6 | 68.3 | Right | Former | Non-diabetic |
| KCV2-023 | Female | 76 | Caucasian | 175 | 72.9 | Left | Never | Diabetic |
| KCV2-024 | Male | 59 | Caucasian | 180 | 66 | Right | Former | Diabetic |
| KCV2-025 | Male | 52 | Caucasian | 175.3 | 81.7 | Left | Current | Non-diabetic |
| | | Mean = 66.2 | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Male – 18<br>Female - 6 | High = 82<br>Low = 43 | Caucasian = 22<br>Hispanic = 1<br>African-American = 1 | High = 190.5<br>Low = 152.4 | High = 170<br>Low = 49.9 | Left = 17<br>Right = 7 | Current = 7<br>Former = 15<br>Never = 2 | Diabetic = 10<br>Non-diabetic = 14 |

| | |
|---|---|
| **Safety Results** | Suspected Adverse events and adverse events were recorded during the study at various visits. None of the major the events reported below can be attributed directly to the product or the treatment procedure by the PI.<br>The firm concludes that the product /treatment is safe to use as intended in future studies. |

**Table 4**: (AEs and SAEs, detailed presentation with start and end dates)

| SUBJECT | START DATE | DESRIPTION | SAE OR AE | END DATE |
|---|---|---|---|---|
| | 5/21/2014 | Left foot Debridement | SAE | 5/21/2014 |
| | 5/23/2014 | Incision & Drainage of Left foot/IN OR | SAE | 5/24/2014 |
| KCV2-001 | 8/19/2014 | Left foot osteomyelitis/left & transmetatarsal Amputation | SAE | 8/25/2014 |
| | 1/28/2015 | Non-healing ulcer Right foot/great toe amputation | SAE | 1/31/2015 |
| | 12/18/2014 | Right Femoral popliteal Bypass with saphenious vein graft Right common iliac vent placement -hospital | SAE | 12/21/2014 |
| | 4/22/2014 | severe ischemic gangrene with necrosis & infection Left BKA | SAE | 4/26/2014 |
| | 4/23/2014 | anemia 5.4 /TU PRBC OP | AE | 4/23/2014 |
| | 7/11/2014 | Non-healing Left BKA site wound /Hospital revision of Left BKA | SAE | 7/14/2014 |
| KCV2-002 | 9/22/2014 | Non-healing Left BKA/Admit skin graft | SAE | 9/23/2014 |
| | 8/27/2014 | cellulities, uncontrolled pain/Admit IVAB, IV pain control | SAE | 9/3/2014 |
| | 9/7/2014 | recurrent cellulities/Hosp IVAB pain mgmt. | SAE | 9/12/2014 |
| | 9/16/2014 | recurrent dependent ruber R/T PAD/ Admit IVAB | SAE | 9/18/2014 |
| | 2/16/2015 | 1)Increase pain, edema/ In Patient referred to HB.2) New Left 3 RD toe with ischemic ulcer | SAE | 2/18/2015 |
| KCV2-003 | 3/11/2015 | Intractable pain/admit LF BKA | SAE | 3/26/2015 |
| KCV2-004 | 5/20/2014 | Anemia /In Patient TU PRBC & IV ferritin | SAE | 5/23/2014 |

| | | | | |
|---|---|---|---|---|
| | 6/6/2014 | Anemia, dehydration/Admit IV fluids | SAE | 6/6/2014 |
| | 6/10/2014 | Cellulitis & Temp/ PO ABX IN PATIENT | SAE | 6/13/2014 |
| | 6/19/2014 | LF wound Infection/Admit LBKA | SAE | 6/23/2014 |
| | 9/9/2014 | Fever non healing surgical wound/PO ABX Out Patient | AE | 9/10/2014 |
| | 9/10/2014 | Non-healing BKA incision - Out Patient | AE | 9/10/2014 |
| | 9/17/2014 | Osteo UE/Admit LBKA revision | SAE | 9/20/2014 |
| | 12/6/2014 | stump infection/surgical revision. Left Knee disarticulation | SAE | 12/12/2014 |
| | 12/15/2014 | Rt hand trauma/Fell seen in ER released | AE | 12/15/2015 |
| | 12/22/2014 | chest pain, SOB/Admit - placed on Beta -blocker echo-cardiac catheter with no intervention | SAE | 12/25/2014 |
| | 2/15/2015 | Rt upper Ext DVT, restarted warfarin (in hospital) | SAE | 2/23/2015 |
| KCV2-005 | 2/6/2015 | ABD pain/Admit - colon ostomy Resection | SAE | 2/23/2015 |
| | 8/26/2014 | LL Critical Limb ischemia/Admit IV AB-IV pain med, IV Anticoagulant Removed Thrombus | SAE | 8/29/2014 |
| | 9/17/2014 | high Platelet - 1 unit Phlebectomy | AE | 9/17/2014 |
| | 9/28/2014 | Increased pain of Non-index foot/ER-IV pain, Meds with pain Mgmt. | AE | 9/28/2014 |
| KCV2-006 | 10/2/2014 | limb dry gangrene with infect/BKA | SAE | 10/7/2014 |
| KCV2-007 | . | none mentioned | | |
| KCV2-008 | 7/2/2014 | Hypotension secondary to sedation requiring 250 cc NS bolus | AE | 7/2/2014 |
| | 10/3/2014 | one visit with primary care | AE | 10/3/2014 |
| | 12/8/2014 | visit with PCP x1 | AE | 12/8/2014 |
| KCV2-009 | 3/26/2015 | Eye infection placed on antibiotics X 10 days, Abnormal mammogram left breast | N/A | No record |
| | 10/2/2014 | Multiple iliac crest access | N/A | |
| KCV2-010 | 11/6/2014 | PCP, Endo, ID, visit | N/A | |
| KCV2-011 | 11/25/2014 | Respiratory infection/Admit pneumonia | SAE | 11/26/2014 |
| KCV2-012 | 11/13/2014 | shoulder pain/Admit Rotation cuff Repair NOT AN ADMISSION | AE | 11/14/2014 |
| KCV2-013 | | none mentioned | | |
| KCV2-014 | 7/29/2015 | Patient having left foot pain been seeing podiatry for neuroma's, currently getting injections to "kill nerve" | AE | 9/1/2015, 7/29/15-9/1/2015 |
| KCV2-015 | 8/2/2015 | hypoxia/admitted Pneumonia CXP-IVAB | SAE | 8/6/2015 |

| | | | | |
|---|---|---|---|---|
| | 8/2/2015 | Bursitis-cellulitis / aspiration of Bursitis Admitted IVAB | SAE | 8/6/2015 |
| | 11/13/2015 | Pneumonia | SAE | 11/14/2015 |
| | 1/3/2016 | C-Diff Colitis (abdominal pain / diarrhea) | SAE | 2/27/2016 |
| | 1/3/2016 | gross hematuria | SAE | ongoing @ study exit |
| | 2/19/2016 | Increased drainage LLE wound | SAE | ongoing @ study exit |
| | 2/19/2016 | UTI & hematuria | SAE | ongoing @ study exit |
| | 2/19/2016 | Sepsis | SAE | 2/27/2016 |
| KCV2-016 | . | none mentioned | | |
| | 5/28/2015 | Hgb 7.6 - low labs value - | AE | 6/24/2015 |
| | 6/4/2015 | Rt groin Hematoma Ultrasound | AE | 6/16/2015 |
| | 7/14/2015 | Intractable foot pain/admitted med adjust | SAE | 8/27/2015 |
| | 8/14/2015 | Intractable foot pain/Hosp pain control | SAE | 8/27/2015 |
| | 8/26/2015 | progresses demarcation of left foot with infection/Hosp BKA | SAE | 8/27/2015 |
| KCV2-017 | 9/1/2015 | s/p LBKA painful Rt toenails/Rehab - toenail debrided | AE | 9/2/2015 |
| | 8/6/2015 | Rt Groin wound /Bactrim Out Patient | AE | 8/16/2015 |
| | 8/21/2015 | UTI - Bactrim | AE | 10/21/2015 |
| KCV2-018 | 1/3/2016 | New pressure ulcer - referred to podiatry- 0.4 cm wound X 0.1 cm deep Φerudite, healthy wound bed foam applied & to follow up with Podiatry. | AE | ongoing @ study exit |
| | 4/2/2016 | respiratory failure | SAE | 4/9/2016 |
| KCV2-019 | 4/9/2016 | L groin pain - possible inguinal hernia | AE | 4/10/2016 |
| | 12/30/2015 | New wound LF heal & toe - Referred to wound clinic | AE | 4/8/2016 |
| | 12/30/2015 | worsening wound - referred to HBO | AE | 4/8/2016 |
| | 4/6/2016 | patient in hospital below BKA on index limb | SAE | 4/8/2016 |
| KCV2-020 | 7/13/2016 | ongoing L BKA wound dehiscence | SAE | ongoing @ study exit |
| | 10/7/2015 | post procedural bleeding / 2 units FFP | SAE | 10/7/2015 |
| | 10/10/2015 | uncontrolled pain / mod start on PCP Fentanyl patch | AE | 10/11/2015 |
| | 10/16/2015 | R leg cellulitis | SAE | 11/12/2015 |
| | 10/19/2015 | Supratheraputic INR / Admit | SAE | 10/20/2015 |
| | 10/19/2015 | Anemia - Hospital PRBC picc placed | SAE | 10/26/2015 |
| | 10/22/2015 | Shortness of breath with anemia | SAE | 10/23/2015 |
| KCV2-021 | 10/30/2015 | mental status changes | SAE | 10/30/2015 |

| | | | | |
|---|---|---|---|---|
| | 10/30/2015 | increased pain & increased edema rle | SAE | 10/31/2015 |
| | 11/2/2015 | Altered mental status -admit med adjust | SAE | 11/5/2015 |
| | 3/9/2016 | Open transmetatarsal amputation of index limb for ischemic ulcer with gangrene | SAE | ongoing @ study exit |
| | 4/15/2016 | worsening of R forefoot ulcer with revision of R forefoot | SAE | ongoing @ study exit |
| | 5/20/2016 | c-diff colitis | SAE | 5/27/2016 |
| | 5/25/2016 | Hospitalized at NKCH for non-healing right foot transmetatarsal amputation site) | SAE | ongoing @ study exit |
| | 8/19/2016 | Split thickness skin graft to R foot | SAE | ongoing @ study exit |
| | 11/7/2016 | admitted for hip fracture after fall | SAE | ongoing @ study exit |
| KCV2-023 | | none mentioned | | |
| KCV2-024 | 4/7/2016 | Diagnostic Colonoscopy for continued GI disturbance & diarrhea | AE | 4/7/2016 |
| KCV2-025 | 4/28/2016 | Subject bit by a pit bull while fixing AC. States he went to a doctor where it happened & no antibiotic or dressing changes given | AE | 4/28/2016 |

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**Table 4a: Overall Summary of Treatment Emergent Adverse Events (TEAE)**

**Analysis Set: All Randomized Subjects**

| | Autologous Stem Cell Transplant 01 (N=24) |
|---|---|
| **Subjects with TEAEs** | |
| **Yes** | **20 ( 83.3%)** |
| **No** | **4 ( 16.7%)** |
| **Subjects with TESAEs** | |
| **No** | **12 ( 50.0%)** |
| **Yes** | **12 ( 50.0%)** |

**Table 4 (a): Treatment Emergent Adverse Events (TEAE) by MedDRA Primary System Organ Class and Preferred Term**

**Analysis Set: All Subjects**

| System Organ Class<br>Preferred Term | Autologous Stem Cell Transplant 01<br>(N=24) |
|---|---|
| Subjects with TEAEs | 20 ( 83.3%) |
| Total Number of TEAEs | 79 |
| Blood and lymphatic system disorders | 3 ( 12.5%) |
| Anaemia | 3 ( 12.5%) |
| Cardiac disorders | 1 ( 4.2%) |
| Angina pectoris | 1 ( 4.2%) |
| Gastrointestinal disorders | 3 ( 12.5%) |
| Abdominal pain | 1 ( 4.2%) |
| Gastrointestinal disorder | 1 ( 4.2%) |
| Inguinal hernia | 1 ( 4.2%) |
| General disorders and administration site conditions | 2 ( 8.3%) |
| Pain | 2 ( 8.3%) |
| Infections and infestations | 9 ( 37.5%) |
| Bursitis infective | 1 ( 4.2%) |
| Cellulitis | 3 ( 12.5%) |
| Clostridium difficile colitis | 2 ( 8.3%) |
| Eye infection | 1 ( 4.2%) |
| Localised infection | 1 ( 4.2%) |
| Osteomyelitis | 1 ( 4.2%) |
| Pneumonia | 2 ( 8.3%) |
| Postoperative wound infection | 1 ( 4.2%) |
| Sepsis | 1 ( 4.2%) |
| Urinary tract infection | 2 ( 8.3%) |
| Wound infection | 1 ( 4.2%) |
| Injury, poisoning and procedural complications | 9 ( 37.5%) |
| Animal bite | 1 ( 4.2%) |
| Hip fracture | 1 ( 4.2%) |
| Limb injury | 2 ( 8.3%) |
| Post procedural complication | 2 ( 8.3%) |
| Post procedural haemorrhage | 1 ( 4.2%) |
| Postoperative wound complication | 2 ( 8.3%) |
| Procedural hypotension | 1 ( 4.2%) |
| Wound | 2 ( 8.3%) |
| Wound dehiscence | 1 ( 4.2%) |
| Investigations | 3 ( 12.5%) |

| | |
|---|---|
| Haemoglobin decreased | 1 ( 4.2%) |
| International normalised ratio increased | 1 ( 4.2%) |
| Platelet count increased | 1 ( 4.2%) |
| Musculoskeletal and connective tissue disorders | 4 ( 16.7%) |
| Musculoskeletal pain | 1 ( 4.2%) |
| Pain in extremity | 3 ( 12.5%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 ( 4.2%) |
| Neuroma | 1 ( 4.2%) |
| Psychiatric disorders | 1 ( 4.2%) |
| Mental status changes | 1 ( 4.2%) |
| Renal and urinary disorders | 1 ( 4.2%) |
| Haematuria | 1 ( 4.2%) |
| Respiratory, thoracic and mediastinal disorders | 2 ( 8.3%) |
| Dyspnoea | 1 ( 4.2%) |
| Respiratory failure | 1 ( 4.2%) |
| Skin and subcutaneous tissue disorders | 5 ( 20.8%) |
| Decubitus ulcer | 1 ( 4.2%) |
| Onychalgia | 1 ( 4.2%) |
| Skin ulcer | 3 ( 12.5%) |
| Surgical and medical procedures | 7 ( 29.2%) |
| Bone operation | 1 ( 4.2%) |
| Debridement | 1 ( 4.2%) |
| Incisional drainage | 2 ( 8.3%) |
| Leg amputation | 2 ( 8.3%) |
| Office visit | 1 ( 4.2%) |
| Skin graft | 1 ( 4.2%) |
| Specialist consultation | 1 ( 4.2%) |
| Vascular operation | 1 ( 4.2%) |
| Vascular disorders | 4 ( 16.7%) |
| Deep vein thrombosis | 1 ( 4.2%) |
| Dry gangrene | 1 ( 4.2%) |
| Haematoma | 1 ( 4.2%) |
| Peripheral arterial occlusive disease | 1 ( 4.2%) |
| Peripheral ischaemia | 1 ( 4.2%) |

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Table 4b: Treatment Emergent Serious Adverse Events (TESAE) by MedDRA Primary System Organ Class and Preferred Term

Analysis Set: All Subjects

| System Organ Class | Autologous Stem Cell Transplant |
|---|---|

01

| Preferred Term | (N=24) |
|---|---|
| Subjects with TESAEs | 12 ( 50.0%) |
| Total Number of TESAEs | 53 |
| Blood and lymphatic system disorders | 2 ( 8.3%) |
| Anaemia | 2 ( 8.3%) |
| Cardiac disorders | 1 ( 4.2%) |
| Angina pectoris | 1 ( 4.2%) |
| Gastrointestinal disorders | 1 ( 4.2%) |
| Abdominal pain | 1 ( 4.2%) |
| General disorders and administration site conditions | 1 ( 4.2%) |
| Pain | 1 ( 4.2%) |
| Infections and infestations | 7 ( 29.2%) |
| Bursitis infective | 1 ( 4.2%) |
| Cellulitis | 3 ( 12.5%) |
| Clostridium difficile colitis | 2 ( 8.3%) |
| Localised infection | 1 ( 4.2%) |
| Osteomyelitis | 1 ( 4.2%) |
| Pneumonia | 2 ( 8.3%) |
| Postoperative wound infection | 1 ( 4.2%) |
| Sepsis | 1 ( 4.2%) |
| Urinary tract infection | 1 ( 4.2%) |
| Wound infection | 1 ( 4.2%) |
| Injury, poisoning and procedural complications | 4 ( 16.7%) |
| Hip fracture | 1 ( 4.2%) |
| Limb injury | 1 ( 4.2%) |
| Post procedural complication | 2 ( 8.3%) |
| Post procedural haemorrhage | 1 ( 4.2%) |
| Postoperative wound complication | 1 ( 4.2%) |
| Wound dehiscence | 1 ( 4.2%) |
| Investigations | 1 ( 4.2%) |
| International normalised ratio increased | 1 ( 4.2%) |
| Musculoskeletal and connective tissue disorders | 2 ( 8.3%) |
| Pain in extremity | 2 ( 8.3%) |
| Psychiatric disorders | 1 ( 4.2%) |
| Mental status changes | 1 ( 4.2%) |
| Renal and urinary disorders | 1 ( 4.2%) |
| Haematuria | 1 ( 4.2%) |

| | |
|---|---|
| Respiratory, thoracic and mediastinal disorders | 2 ( 8.3%) |
| Dyspnoea | 1 ( 4.2%) |
| Respiratory failure | 1 ( 4.2%) |
| Skin and subcutaneous tissue disorders | 3 ( 12.5%) |
| Skin ulcer | 3 ( 12.5%) |
| Surgical and medical procedures | 5 ( 20.8%) |
| Surgical and medical procedures (Continued) | |
| Debridement | 1 ( 4.2%) |
| Incisional drainage | 1 ( 4.2%) |
| Leg amputation | 2 ( 8.3%) |
| Skin graft | 1 ( 4.2%) |
| Vascular operation | 1 ( 4.2%) |
| Vascular disorders | 3 ( 12.5%) |
| Deep vein thrombosis | 1 ( 4.2%) |
| Dry gangrene | 1 ( 4.2%) |
| Peripheral arterial occlusive disease | 1 ( 4.2%) |
| Peripheral ischaemia | 1 ( 4.2%) |

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Table 4c: Treatment Emergent Serious Adverse Events (TESAE) by MedDRA Primary System Organ Class and Preferred Term

Analysis Set: All Subjects

| System Organ Class<br>01<br>Preferred Term | Autologous Stem Cell Transplant<br><br>(N=24) |
|---|---|
| Subjects with TESAEs | 12 ( 50.0%) |
| Total Number of TESAEs | 53 |
| Blood and lymphatic system disorders | 2 ( 8.3%) |
| Anaemia | 2 ( 8.3%) |
| Cardiac disorders | 1 ( 4.2%) |
| Angina pectoris | 1 ( 4.2%) |
| Gastrointestinal disorders | 1 ( 4.2%) |
| Abdominal pain | 1 ( 4.2%) |
| General disorders and administration site conditions | 1 ( 4.2%) |
| Pain | 1 ( 4.2%) |
| Infections and infestations | 7 ( 29.2%) |
| Bursitis infective | 1 ( 4.2%) |
| Cellulitis | 3 ( 12.5%) |

| | |
|---|---|
| Clostridium difficile colitis | 2 ( 8.3%) |
| Localised infection | 1 ( 4.2%) |
| Osteomyelitis | 1 ( 4.2%) |
| Pneumonia | 2 ( 8.3%) |
| Postoperative wound infection | 1 ( 4.2%) |
| Sepsis | 1 ( 4.2%) |
| Urinary tract infection | 1 ( 4.2%) |
| Wound infection | 1 ( 4.2%) |
| Injury, poisoning and procedural complications | 4 ( 16.7%) |
| Hip fracture | 1 ( 4.2%) |
| Limb injury | 1 ( 4.2%) |
| Post procedural complication | 2 ( 8.3%) |
| Post procedural haemorrhage | 1 ( 4.2%) |
| Postoperative wound complication | 1 ( 4.2%) |
| Wound dehiscence | 1 ( 4.2%) |
| Investigations | 1 ( 4.2%) |
| International normalised ratio increased | 1 ( 4.2%) |
| Musculoskeletal and connective tissue disorders | 2 ( 8.3%) |
| Pain in extremity | 2 ( 8.3%) |
| Psychiatric disorders | 1 ( 4.2%) |
| Mental status changes | 1 ( 4.2%) |
| Renal and urinary disorders | 1 ( 4.2%) |
| Haematuria | 1 ( 4.2%) |
| Respiratory, thoracic and mediastinal disorders | 2 ( 8.3%) |
| Dyspnoea | 1 ( 4.2%) |
| Respiratory failure | 1 ( 4.2%) |
| Skin and subcutaneous tissue disorders | 3 ( 12.5%) |
| Skin ulcer | 3 ( 12.5%) |
| Surgical and medical procedures | 5 ( 20.8%) |
| Surgical and medical procedures (Continued) | |
| Debridement | 1 ( 4.2%) |
| Incisional drainage | 1 ( 4.2%) |
| Leg amputation | 2 ( 8.3%) |
| Skin graft | 1 ( 4.2%) |
| Vascular operation | 1 ( 4.2%) |
| Vascular disorders | 3 ( 12.5%) |
| Deep vein thrombosis | 1 ( 4.2%) |
| Dry gangrene | 1 ( 4.2%) |
| Peripheral arterial occlusive disease | 1 ( 4.2%) |
| Peripheral ischaemia | 1 ( 4.2%) |

**Table 5**: Major and Minor Amputations Entire Study Amputations after Dosing

| Subject ID | Age (yrs) | Rutherford Scale on Enrolled Day | Date of Dosing | Date of Amputation | Type of Amputation (Major/Minor) | Remarks | Time from dosing (Days) | Primary objective effect |
|---|---|---|---|---|---|---|---|---|
| KCV2-001 | 81 | 5 | 02/20/14 | 8/19/2014 | Minor | Left trans-metatarsal amputation (TMA) | 180 | None |
| KCV2-002 | 54 | 5 | 03/20/14 | 1/31/2015 | Minor | Right great toe amputation | 317 | None |
| KCV2-002 | | | | 4/22/2014 | Major | LBKA | 33 | Fail |
| KCV2-003 | 50 | 4 | 04/03/14 | 3/1/2015 | Major | LBKA* | 332 | None |
| KCV2-004 | 59 | 5 | 04/24/14 | 6/19/2014 | Major | LBKA | 56 | Fail |
| KCV2-006 | 50 | 5 | 06/05/14 | 10/30/2014 | Major | LBKA | 147 | None |
| KCV2-017 | 72 | 4 | 05/20/15 | 8/26/2015 | Major | LBKA | 98 | None |
| KCV2-020 | 68 | 4 | 09/30/15 | 4/6/2016 | Major | LBKA | 189 | None |
| KCV2-021 | 66 | 5 | 10/07/15 | 3/9/2016 | Minor | Right trans-metatarsal amputation (TMA) | 154 | None |

PIs Note: Per Dr. Stark the PI, in some AKA (Above Knee Amputation) was prevented –due to increased vascularity in the limb area
* LBKA: Left Below Knee Amputation

**Table 6:** ASCT01 Stem Cell Product Information - patients KCV2-001 to KCV2-025

| Patient ID | Bone Marrow Aspirated Volume mL (iliac Crest both sides) | Conc. ASCT01 Stem cell Processed by Lifecells | ASCT01 Final Volume at 10 million cells/mL Prepared by Lifecells | Administered by IA catheter infusion at 5 ml/minute with Braun metered infusion pump-80% | Administered by IM injections along the neurovascular bundle - 20% -6 to 40 injections divided into equal volumes in OR | Total CD45+ Cells Billions | CD45+ Cells/mL Millions | Total CD34+CellsMillion | CD45+Cell Viability |
|---|---|---|---|---|---|---|---|---|---|
| KCV2-001 | 220 | 3.5 | 137 | 110 | 27 | 2.5 | 18.4 | 42.7 | 76 |
| KCV2-002 | 223 | 6.0 | 175 | 143 | 32 | 2.0 | 11.2 | 24.2 | 90.2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| KCV2-003 | 207 | 5.0 | 121 | 96 | 25 | 1.2 | 9.8 | 13.1 | 88.3 |
| KCV2-004 | 203 | 3.0 | 264 | 209 | 55 | 1.7 | 6.3 | 12 | 89.4 |
| KCV2-005 | 211 | 6.3 | 562 | 452 | 110 | 4.3 | 7.7 | 156.7 | 76.1 |
| KCV2-006 | 231 | 4.0 | 81 | 65 | 16 | 0.8 | 9.3 | 23.4 | 78.4 |
| KCV2-007 | 200 | 6.0 | 384 | 306 | 78 | 2.4 | 6.4 | 33.3 | 74.6 |
| KCV2-008 | 200 | 4.8 | 165 | 130 | 35 | 1.4 | 8.7 | 50.2 | 74.9 |
| KCV2-009 | 217 | 5.0 | 480 | 383 | 97 | 3.7 | 7.6 | 31.9 | 78.4 |
| KCV2-010 | 161 | 2.8 | 68 | 54 | 14 | 0.4 | 6.6 | 9.4 | 69.3 |
| KCV2-011 | 202 | 2.3 | 69 | 55 | 14 | 0.7 | 10.6 | 6.7 | 88.5 |
| KCV2-012 | 239 | 4.5 | 164 | 131 | 33 | 1.6 | 9.7 | 22 | 95 |
| KCV2-013 | 209 | 2.5 | 88 | 70 | 18 | 0.9 | 10.4 | 13.8 | 97.4 |
| KCV2-014 | 203 | 3.4 | 137 | 108.5 | 28.5 | 1.4 | 10.4 | 19.5 | 93.3 |
| KCV2-015 | 218 | 2.5 | 154 | 123 | 31 | 1.3 | 8.7 | 21.9 | 92.5 |
| KCV2-016 | 244 | 4.0 | 237 | 189 | 48 | 2.2 | 9.4 | 31.8 | 97.2 |
| KCV2-017 | 235 | 3.0 | 126 | 100 | 26 | 1.2 | 9.5 | 7.7 | 94.8 |
| KCV2-018 | 264 | 2.0 | 84 | 68 | 16 | 0.5 | 5.4 | 6.3 | 96 |
| KCV2-019 | 247 | 1.0 | 47.6 | 38 | 9.5 | 0.3 | 7.1 | 4.4 | 96 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| KCV2-020 | 210 | 2.5 | 117.5 | 94 | 23.5 | 0.4 | 3.8 | 5 | 89.4 |
| KCV2-021 | 223 | 3.3 | 160 | 128 | 32 | 1.8 | 11.1 | 15.9 | 98.3 |
| KCV2-023 | 227 | 2.8 | 183.5 | 146 | 37.5 | 1.9 | 10.5 | 29.6 | 97.3 |
| KCV2-024 | 224 | 2.0 | 88 | 70 | 18 | 1.0 | 11.6 | 8.9 | 96.7 |
| KCV2-025 | 195 | 3.0 | 156.5 | 125 | 31.5 | 1.6 | 10.4 | 14.3 | 95 |
| Range | 161 to 264 | 1 to 6.25 | 47.6 to 562 | 38 to 452 | 9.5 to 110 | 0.3 to 4.3 | 3.8 to 18.4 | 4.4 to 156.7 | 69.3 to 98.3 |

| | |
|---|---|
| **Conclusion** | The 12-month follow-up has shown that the test treatment was safe and well tolerated by all the study patients administered as single treatment. Efficacy outcome of over 50% was observed in this CLI study. On this basis, the sponsor intends to complete a pivotal phase 3 study after review and discussion with the Agency |
| **DATE OF THE REPORT** | August 4, 2017 |