CLINICAL STUDY PROTOCOL

MultiStem® Administration for Stroke Treatment and Enhanced Recovery Study (MASTERS-2)

Investigational Product: MultiStem
Protocol Number: B01-04
EudraCT Number: 2019-001680-69
IND Number: 13852

Sponsor:
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SIGNATURE PAGE

STUDY TITLE: MultiStem® Administration for Stroke Treatment and Enhanced Recovery Study (MASTERS-2)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature | Date

Digitally signed by Robert W. Mays
Date: 2020.03.26 13:52:49 -04'00'

Robert W. Mays, PhD
Vice President Regenerative Medicine
Head of Neuroscience
Athersys, Inc.

27 March 2020

Eric D. Jenkins, MD
Medical Director
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INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Athersys, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Athersys, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Athersys, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: MultiStem® Administration for Stroke Treatment and Enhanced Recovery Study (MASTERS-2)

PROTOCOL NUMBER: B01-04

INVESTIGATIONAL PRODUCT: MultiStem

PHASE: 3

INDICATION: MultiStem is an allogeneic, regenerative medicine advanced therapy indicated for treatment of acute ischemic stroke within 36 hours after symptom onset.

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy of MultiStem on functional outcome in subjects with ischemic stroke.

The secondary objectives of this study are the following:

- To evaluate the efficacy of MultiStem on functional, neurological, mortality, secondary infection, and hospitalization outcomes in subjects with ischemic stroke; and
- To evaluate the safety of MultiStem in subjects with ischemic stroke.

The tertiary objectives of this study are the following:

- To evaluate the impact of MultiStem on quality of life and healthcare and rehabilitation services utilization in subjects with ischemic stroke; and
- To evaluate the mechanism of action of MultiStem through blood biomarkers, and spleen and brain imaging outcomes in subjects with ischemic stroke.

POPULATION:

Inclusion criteria

Subjects will be eligible for the study if they meet all of the following inclusion criteria:

1. Male or female subjects 18 years of age or older;
2. Clinical diagnosis of ischemic stroke involving cerebral cortex;
    - This inclusion criterion requires clinical signs that are consistent with imaging abnormalities required under inclusion criterion #5. Clinical diagnosis is defined as rapidly developed clinical signs of 1 or more focal (and potentially accompanying global) persistent disturbance(s) of cerebral function, with no apparent cause other than arterial occlusive ischemic stroke that involves cerebral cortex;

3. Onset of stroke symptoms must have occurred 18 to 36 hours prior to the planned start of administration of the investigational product;

   Note: Time of onset is defined as the time point, if known, when symptoms first began. For a stroke that occurred during sleep, or in an individual unable to report the time that symptoms began, the time of onset is defined as the time point when the subject was last observed to exhibit normal neurological function or was self-reported to have normal function;

4. Occurrence of a moderate to moderately severe stroke with a persistent neurologic deficit documented by a National Institutes of Health Stroke Scale (NIHSS) score of 8 to 20 (inclusive) that does not change by ≥4 points from the Screening to the Baseline assessment;

   Note: The Screening NIHSS score used for determination of eligibility should be collected as soon as possible following admission to the hospital. In the event a subject receives concomitant reperfusion therapy the subject's Screening NIHSS score is encouraged to be collected prior to any concomitant reperfusion therapy but can be collected as late as 4 hours following completion of the last reperfusion (mechanical or pharmacologic) therapy;

5. Confirmation of hemispheric cortical infarct by brain magnetic resonance imaging (MRI) or computed tomography (CT) demonstrating an acute ischemic infarct measuring ≥5 mL and ≤100 mL;

6. A modified Rankin Scale (mRS) score of 0 or 1 prior to the onset of symptoms of the current stroke, by either self-reported history or by family/caregiver report;

7. Female subjects must not be pregnant, breastfeeding, or planning on becoming pregnant during the study; and either:

   a. Not of childbearing potential, defined as one who has been postmenopausal for at least 1 year, or has been surgically sterilized; or

   b. Agree to use a medically accepted, effective method of avoiding pregnancy through the Day 90 Visit. Effective methods of contraception are defined as those that result in a low failure rate (<1% per year) when used consistently and correctly. Such methods include the use of oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products (such as an intrauterine diaphragm, condoms, or spermicides);

8. Male subjects with female sexual partners of childbearing potential must also agree to use an effective method of avoiding pregnancy through the Day 90 Visit;

9. Subjects or legally authorized representatives (LARs) must freely sign the informed consent form after the nature of the study and the disclosure of his/her data have been explained;

10. Willing and able to comply with all aspects of the treatment and testing schedule; and

11. Willing and able to return to the study site for the post-treatment evaluations.

Exclusion criteria

Subjects will not be eligible for the study if they meet any of the following exclusion criteria:

1. Presence of a lacunar or a brainstem infarct on MRI or CT as the etiology of current stroke symptoms;

2. Coma (score of 3 for item 1a of NIHSS);
3. Occurrence of a hemorrhagic transformation of ischemic stroke as evidenced by brain MRI or CT that is clinically significant in the opinion of the Investigator;
4. Fluctuation in neurologic status since the onset of stroke suggesting possible progression or expansion of stroke, transient ischemic attack, or stroke mimic;
5. Onset of stroke >28 hours prior to the start of Screening;

   Note: Onset of stroke >28 hours prior to the start of Screening would not allow for administration of investigational product per protocol;
6. Less than 6 hours between the Screening and Baseline NIHSS assessment;
7. Initiation of intravenous (IV) tissue plasminogen activator (tPA) infusion >4.5 hours and/or mechanical reperfusion (MR) (defined as time of groin puncture) >8 hours after the onset of stroke;

   Note: tPA implies not only recombinant human tissue plasminogen activator, but also its engineered derivatives, including tenecteplase, Retavase®, and potentially other such agents that might conceivably reach the market (once they are approved and including desoteplase, lanoteplase, etc.);
8. Plan to have a neurovascular procedure (e.g., carotid endarterectomy, stent placement, etc.) within the first year following stroke;
9. Pre-existing ipsilateral focal neurologic deficits that would complicate evaluation;
10. Seizure since the onset of stroke or prior history of seizures, with the exception of simple febrile seizures in childhood;
11. Major neurologic event such as stroke or clinically significant head trauma in the 6 months preceding study entry;
12. Uncontrolled hypertension prior to randomization, defined as persistent systolic blood pressure >220 mmHg or diastolic blood pressure >120 mmHg despite antihypertensive therapy;
13. Blood glucose level <50 mg/dL or >350 mg/dL prior to randomization despite concomitant therapy;
14. Significant comorbid medical condition(s), including, but not limited to:
    a. End-stage renal disease requiring renal replacement therapy;
    b. Advanced liver disease (e.g., Childs-Pugh score >10);
    c. Severe congestive heart failure (e.g., New York Heart Association score of III or IV) or ejection fraction <30%;
    d. Severe lung disease requiring continuous home oxygen; or
    e. Symptomatic refractory angina requiring daily treatment with nitrates or other medications;
15. Concurrent systemic infection or severe local infection;

16. Immunocompromised state due to immunosuppressive medications or as evidenced by hematologic studies or history of opportunistic infection;
17. History of Alzheimer's disease or other dementias, Parkinson's disease, or any other neurological disorder that in the opinion of the Investigator would affect the subject's ability to participate in the study or confound study assessments;
18. History of malignancy of any type within 2 years of stroke onset, with the exception of adequately treated basal or squamous cell carcinoma of the skin;
19. Life expectancy less than 90 days;
20. Prior surgical removal of the spleen or functional asplenia;
21. Allergy or religious objections to human tissue or bovine or porcine products;
22. Participation in any other study involving an investigational product or device within the last 30 days or planned participation in investigational rehabilitation stroke recovery program; or
23. Other serious medical or psychiatric illness that is not adequately controlled and, in the Investigator's opinion, would not permit the subject to be managed or evaluated according to the protocol.

STUDY DESIGN AND DURATION:

This is a pivotal Phase 3, randomized, double-blind, placebo-controlled, multicenter international study. The total study duration for safety follow-up will be 12 months. Approximately 300 subjects who have experienced an acute cortical ischemic stroke and fulfill all the eligibility criteria will be enrolled into the study globally.

Approximately 300 subjects will be randomized in a 1:1 ratio (MultiStem [n=150] or placebo [n=150]) to receive a single IV infusion of 1.2 billion cells of MultiStem. Randomization will be stratified by Baseline NIHSS score (≤12 and ≥13), concomitant reperfusion therapy (Yes or No), and age (18 to 64 and ≥65 years). All subjects will be enrolled continuously into the study. Enrollment of subjects receiving concomitant reperfusion therapy (tPA, MR, or tPA + MR) will be limited to 40% of the entire randomized study population (approximately 120 subjects) with the tPA + MR sub-group being limited to 10% of the entire randomized study population.

Protocol stopping rules will be in place, with an independent Data Safety Monitoring Board (DSMB) assembled if serious safety events, including infusion reactions, occur related to investigational product. In addition, the DSMB will meet during the subject enrollment period to examine the unblinded safety data.

Subjects will be evaluated at Baseline, prior to infusion and post-infusion, 24 hours from the start of the infusion, 48 hours from the start of the infusion, Day 7, Day 30, Day 90, Day 180, and Day 365, or at the Early Termination Visit. To prevent subjects from being lost to follow-up, study sites will contact subjects every other month (Day 60, Day 150, Day 210, Day 270, and Day 330 [±7 days]) remotely to update the subject's medical status and disposition.

At the Screening Visit, subjects or LARs will provide written informed consent and undergo standard of care procedures, evaluation for inclusion/exclusion criteria, medical history, a physical examination, height and weight, pulse oximetry, concomitant medication assessments, 12-lead

electrocardiogram (ECG), blood safety laboratory assessments, pregnancy testing, vital sign assessments, NIHSS assessment, pre-stroke mRS historical assessment, and brain MRI/CT.

The Screening Barthel Index score can be collected any time prior to the start of the infusion.

At the Baseline Visit (Day 0), subjects will be re-evaluated for inclusion/exclusion criteria, undergo a physical examination, vital signs, pulse oximetry, adverse event (collection begins from the start of the infusion) and concomitant medication assessments, blood safety laboratory collection, allogeneic antibody and exploratory blood biomarker collections, and a NIHSS assessment.

Subjects meeting eligibility requirements will be randomized and receive an IV infusion of MultiStem or placebo (18 to 36 hours post-stroke).

During the study, assessments of safety will include the evaluation of adverse events and concomitant medications, clinical laboratory results, allogeneic antibody testing, vital signs, pulse oximetry, 12-lead ECGs, and physical examinations. Efficacy will be assessed by mRS, NIHSS, Barthel Index, and EuroQol 5 dimensions (EQ-5D) scores. Healthcare and rehabilitation services utilization will be assessed during the study. Exploratory blood biomarkers will be assessed at Baseline and during the study.

Subjects at selected sites will undergo ultrasound of the spleen and brain MRI (diffusion tensor imaging) at Baseline (prior to the start of the infusion) and throughout the study to explore the mechanism of action of MultiStem.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Subjects will be randomly assigned to receive a single IV infusion of MultiStem or matching placebo at Baseline (Day 0 [18 to 36 hours post-stroke]). MultiStem will be provided in a 1.2 billion cell dose ±20%.

EFFICACY VARIABLES:

The primary efficacy variable is the mRS score at Day 90. Differences between the MultiStem and placebo treatment groups in the distribution of Day 90 mRS scores will be evaluated by shift analysis.

The key secondary efficacy variables are defined below. Differences between the MultiStem and placebo treatment groups will be evaluated using hierarchical testing.

- Proportion of subjects achieving an excellent outcome at Day 365 defined by all of the following criteria: mRS score of ≤1, NIHSS total score of ≤1, and Barthel Index score of ≥95;
- Proportion of subjects achieving an excellent outcome at Day 90 defined by all of the following criteria: mRS score of ≤1, NIHSS total score of ≤1, and Barthel Index score of ≥95; and
- Proportion of subjects with a mRS score of ≤2 at Day 90.

Other secondary efficacy variables will examine the difference between the MultiStem and placebo treatment groups for the following:

- Global disability throughout the range of mRS scores by shift analysis at Day 365;
- Proportion of subjects with a Barthel Index score of ≥95 at Day 90 and Day 365;
- Proportion of subjects with a NIHSS score of ≤1 at Day 90 and Day 365;
- Proportion of subjects with a mRS score of ≤1 at Day 90 and Day 365;
- Number of hospital-free days through Day 28;
- Number of intensive care unit-free days through Day 28;
- Number of hospital-free days through Day 90;
- Number of hospital and non-hospital residential care-free days through Day 90;
- Proportion of subjects with all-cause mortality through Day 90;
- Proportion of subjects with secondary infections through Day 90;
- Proportion of subjects with urinary tract infections through Day 90; and
- Proportion of subjects who survived without life-threatening adverse events at Day 90.

Tertiary efficacy variables include the difference between the MultiStem and placebo treatment groups for the following:

- Changes in blood biomarkers (white blood cell populations and inflammatory markers) from Baseline to 48 hours from the start of the infusion and Day 7;
- Quality of life measured by the EQ-5D questionnaire at Day 90 and Day 365;
- Number of hospital and non-hospital residential care-free days through Day 365;
- Rehabilitation services utilization through Day 365;
- Changes in spleen size via exploratory imaging from Baseline to 24 hours from the start of the infusion, 48 hours from the start of the infusion and Day 7/discharge (sub-study at selected sites only); and
- Changes in white matter tract organization via exploratory imaging from Baseline to Day 90 and Day 365 (sub-study at selected sites only).

SAFETY VARIABLES:

Safety assessments include adverse events, clinical laboratory evaluations, vital signs (including blood pressure, pulse, respiratory rate, and temperature), oxygen saturation via pulse oximetry, physical examinations, and ECGs.

STATISTICAL ANALYSES:

Details for all analyses will be described in a Statistical Analysis Plan.

Primary efficacy analyses

The primary efficacy variable will be the mRS score at Day 90. To compare the distributions of the mRS scores at Day 90, all mRS values (0 to 6) will be considered (except the categories 5 and 6 are collapsed into a single group). The proportion of subjects in each category will be summarized with counts and percentages and compared between the MultiStem group and placebo group. Specifically, the van Elteren test, an extension of the 2-sample Wilcoxon rank-sum test, stratified by Baseline NIHSS score (≤12 and ≥13), use of concomitant reperfusion therapy (Yes or No), and age group (18 to 64 years and ≥65 years), will be used for the primary comparison. The treatment effect will be quantified following a method proposed by Howard et al.,[16] where each MultiStem subject within a stratum is paired with all placebo subjects in the stratum in order to determine the percentage of subject pairs where MultiStem subjects achieved a better mRS score and the percentage of subject pairs where placebo subjects achieved a better mRS score. The weighted averages (weighted by stratum size) of the stratum-specific percentages will then be calculated and the difference between the 2 probabilities will measure the treatment effect. The confidence interval will be constructed based on large sample approximations for the distribution of related U-statistics.

For the primary analysis, the last observation carried forward (LOCF) approach will be applied to impute missing data, e.g., a missing mRS score at Day 90 will be imputed by the last observed post-Baseline mRS score prior to Day 90. Subjects who die prior to Day 90 will have a mRS score of 6 imputed for the Day 90 analysis.

As a supportive analysis, an alternative measure for the treatment effect, the odds ratio from a stratified proportional odds model, will be estimated as well.

Key secondary efficacy analyses

The key secondary endpoints will be compared between the randomized treatment groups with the overall Type I error controlled using hierarchical testing. Specifically, if statistical significance is observed on the primary effectiveness endpoint, the secondary clinical efficacy endpoints will then be tested in sequential fashion in the order presented, each at a level of 0.05, with testing ceasing once a null hypothesis cannot be rejected.

For each of the key secondary endpoints, the Cochran-Mantel-Haenszel test will be used, stratified by the stratification factors. Treatment differences will be quantified using the difference in the proportion of having favorable outcome.

For each key secondary efficacy analysis, the LOCF approach will be applied to impute missing data. Subjects who die prior to the specified time point will have the worst possible outcome imputed for that analysis.

Safety analyses

In general, safety analyses will be presented by treatment group and overall for the Safety Population.

SAMPLE SIZE DETERMINATION:

For this study, sample size and power are computed by assuming that the true proportions of subjects with various mRS outcomes at the 90-day follow-up visit are as follows:

Estimates of Proportions of Subjects With Modified Rankin Scale Scores – 90-Day Follow-up Visit

	Modified Rankin Scale Score						
Group	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Treatment	4.0%	15.5%	28.9%	26.6%	17.5%	0.0%	7.4%
Control	0.0%	6.8%	27.1%	29.7%	14.4%	5.8%	16.3%

The rates used in the computations correspond to those observed in B01-02 for the population under study in B01-04, making minor adjustments to reflect expectations for subjects receiving both tPA and mechanical thrombectomy (limited to 10% of enrolled B01-04 study subjects). The power of unstratified Wilcoxon rank test was estimated using Monte-Carlo simulation. Based on this approach, a 1-sided alpha level of 0.025, 300 subjects provide 95% power for testing the study's primary effectiveness hypothesis. The power of van Elteren test adjusting for stratification factors will be even higher than this unstratified counterpart.

Other alternative outcome estimates were evaluated (a) adjusting the outcome above by reducing the treatment advantage over control, and (b) comparing an adjusted treatment outcome to placebo rates observed in other relevant studies. Several studies were identified with control populations representative of the targeted population for B01-04, taking into consideration stroke severity, concomitant treatments (e.g., tPA), timing of treatment, age, and functional outcomes.

These sensitivity analyses confirm that at 300 subjects (150 subjects per group), the B01-04 study would be adequately powered to test the hypothesis that MultiStem treatment can improve global disability as measured throughout the range of mRS scores by shift analysis.

Based on previous studies, the proposed study is expected to have a low dropout rate. Outside of death, the discontinuation rate is expected to be approximately 6% to 7%.

SITES: Approximately 50 to 60 sites globally.

SPONSOR:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
CRA	Clinical research associate
CT	Computed tomography
CTA	Clinical trial authorization
CTIRT	ClinTrak® Interactive Response Technology
DSMB	Data Safety Monitoring Board
DTI	Diffusion tensor imaging
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D	EuroQol 5 dimensions
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HLA	Human Leukocyte Antigen
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LAR	Legally authorized representative
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MR	Mechanical reperfusion
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
RMAT	Regenerative medicine advanced therapy
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
tPA	tissue plasminogen activator

1 INTRODUCTION AND BACKGROUND INFORMATION

MultiStem® is a regenerative medicine advanced therapy (RMAT) product originating from adult adherent stem cells taken from the bone marrow of healthy, consenting, non-related donors. The MultiStem product is a proprietary subset of allogeneic bone marrow derived stem cells harvested from a single donor and expanded ex vivo to produce millions of therapeutic doses. MultiStem is being developed and tested for the treatment of ischemic stroke and other indications.[1]

1.1 Background

1.1.1 Stroke

Stroke is a serious life-threatening and frequently profoundly disabling medical condition.[2,3] It is the leading cause of serious disability, and the second highest cause of death in the world, accounting for approximately 10% of deaths globally.[4] There are approximately 33 million people in the world who have experienced a stroke, and are now living with post-stroke morbidity. Each year more than 16 million people suffer their first ischemic stroke, including more than 2 million people in the United States, Japan, and the European Union combined.

Current drug or biologic therapies for stroke are limited. Only one recombinant protein therapy, tissue plasminogen activator (tPA), directed at the dissolution of thrombi in affected blood vessels is currently available. There are no other drugs or biologic treatments currently available for treating ischemic stroke or mitigating the damage these events cause. Mechanical thrombectomy may improve outcomes for some stroke patients, but like tPA, its utility is limited to a short time window following stroke onset, and to certain types of stroke. The numbers of affected individuals, the associated morbidity and mortality, the direct and indirect costs of care, and lost productivity, coupled with the lack of current therapies illustrate the significant unmet medical need that stroke represents.

Cellular therapy for the treatment of stroke is an emerging field of clinical research aimed at developing new treatments for patients for whom very limited therapeutic options exist.[5] Cell therapeutics hold the promise of treating stroke through protection of tissue at risk after the initial ischemic event, as well as support of innate tissue repair processes, thereby improving function by preventing or ameliorating permanent neurologic deficits.

1.1.2 Non-Clinical

Animal data suggest that MultiStem produces trophic factors that may reduce inflammation following ischemic injury and provide protection to at-risk neurons, improve circulation, and indirectly play a role in replacement of damaged cells. Furthermore, non-clinical data demonstrate that single intravenous (IV) doses of MultiStem improve functional performance in rats with ischemic stroke injury in a dose-dependent manner.

MultiStem is thought to work in ischemic stroke through a variety of mechanisms, an important one being the modulation of secondary immune organs such as the spleen.[6] Non-clinical data suggest that MultiStem migrates to the spleen to transiently secrete various proteins and factors to cause immunomodulation of this secondary immune organ resulting in the attenuation of the hyper-immune and inflammatory responses that occur after an injury or ischemic insult such as a stroke. The immunomodulation helps to prevent further damage around the stroke infarct area in the brain by reducing the hyper-inflammatory cascade. Additionally, non-clinical data show that

MultiStem can produce factors that reduce local inflammation, protect ischemic tissue and at-risk cells, reduce fibrotic scar formation, and even promote neurogenesis.[6,7,8,9,10,11,12,13] MultiStem represents a mechanistically novel approach for the treatment of ischemic stroke that has the potential to provide efficacy with a significantly reduced side effect risk profile relative to currently used treatments.

A comprehensive non-clinical toxicology and safety program of Good Laboratory Practice (GLP) and non-GLP studies has been conducted with MultiStem. The results of these studies demonstrated no effects of MultiStem on pulmonary function, cardiovascular safety parameters, or chemistry and hematology parameters along with no evidence of cell-mediated immunogenicity or tumorigenicity with MultiStem use. In addition, standard drugs used to treat ischemic stroke do not affect MultiStem cell viability and function.

The highest single doses studied in these aforementioned non-clinical studies were 40 million MultiStem cells/dose (200 million cells/kg) in rats or 10 million MultiStem cells/dose (500 million cells/kg) in mice. This animal data provides up to an approximate 13-fold safety margin on a per kilogram weight basis over the highest anticipated individual IV dose to be administered in the proposed Phase 3 ischemic stroke clinical study (1.2 billion total cells or 15 million cells/kg/dose based on an 80 kg person). No maximum tolerated dose has yet been established in non-clinical studies, as all doses examined to date have exhibited good safety and tolerability.

1.1.3 Clinical

The previously completed B01-02 Phase 2 study examined a single, 1.2 billion cell dose of MultiStem administered 24 to 48 hours following an acute ischemic stroke. The B01-02 study design was double-blinded, randomized, and placebo-controlled with 134 subjects enrolled/dosed and was conducted at 33 sites in the United States and the United Kingdom.[14] Eligible subjects had to have suffered a cortical cerebral ischemic stroke with moderate to moderately-severe disability (National Institutes of Health Stroke Scale [NIHSS] scores 8 to 20), as measured at Baseline at least 24 hours from the time of stroke onset.

The B01-02 study data showed MultiStem cell therapy to be well tolerated and associated with a favorable impact on a range of complications and outcomes following ischemic stroke.[15] In all subjects treated with 1.2 billion MultiStem cells 24 to 48 hours after stroke onset, the MultiStem group showed a trend for benefit compared to the placebo group in Excellent Outcome at Day 90 (modified Rankin Scale [mRS] ≤1; NIHSS ≤1; and Barthel Index ≥95), and this effect was significant by Day 365. The study also showed that earlier administration (≤36 hours) was associated with significant difference between MultiStem and placebo in the distribution of mRS scores, and higher rates of subjects achieving an Excellent Outcome at Day 90 and/or Day 365. Additionally, early MultiStem treatment (≤36 hours) was associated with accelerated recovery for some subjects, as is evident in the proportion of MultiStem subjects relative to placebo subjects achieving a mRS score of ≤2 or Barthel Index score of ≥95 at Day 30.

Treatment with 1.2 billion MultiStem cells was shown to be safe and generally well tolerated throughout the B01-02 study. Additionally, the results showed MultiStem to be associated with a favorable impact on a range of complications and outcomes following ischemic stroke including a reduced incidence of deaths, life-threatening adverse events, urinary tract infection, and secondary infection rates compared to placebo. Additionally, the mean duration of hospitalization and the

mean duration of stay in an intensive care unit (ICU) were shorter in the MultiStem compared to the placebo group.

Through Year 1, MultiStem-treated subjects in the B01-02 study generally continued to improve compared to placebo subjects, as evident in multiple measures of neurological function.[15] For example, at 90 days, early-treated MultiStem subjects (≤36 hours) had a higher proportion of Excellent Outcomes (i.e., full or nearly full recovery) than placebo subjects (16.1% v. 6.6%). By 1 year, 3.5 times as many of the early-treated MultiStem subjects achieved the Excellent Outcome endpoint compared to placebo subjects (29.0% v. 8.2%, $p<0.01$). Finally, the available data suggest that MultiStem could provide functional and clinical benefit to subjects with moderate and moderately-severe strokes, subjects who have received reperfusion therapy as well as those who have not, and younger and older stroke subjects.

1.2 Rationale

More than 300 subjects have been administered single or multiple doses of MultiStem cell therapy (ranging from approximately 20 million to 1.2 billion total cells) in Phase 1 and 2 clinical studies for acute myocardial infarction, hematopoietic malignancy transplant, liver transplant, ulcerative colitis, acute respiratory distress syndrome, and ischemic stroke. To date, adverse events have been consistent with the disease states being studied in ongoing and completed studies, and MultiStem treatment has been well tolerated (see the Investigator's Brochure for further information).

MultiStem cell therapy for the treatment of ischemic stroke has the potential to target multiple reparative, anti-inflammatory, and cytoprotective processes after stroke onset. MultiStem can be delivered intravenously and has a wider target therapeutic time window than tPA. MultiStem has the potential to provide a new treatment option for patients suffering from this common, life-threatening and disabling condition for which very limited treatment options currently exist. Current therapies have limited efficacy, impart a significant risk of potentially devastating complications, and are administered to only a small minority of ischemic stroke patients due to the limited treatment time window, as well as contraindications and/or restrictions for use.

Overall, the aforementioned clinical and non-clinical data demonstrate that human MultiStem cells have been adequately characterized and supports safe progression into the current Phase 3 study, which will examine the effect of MultiStem cell therapy compared to placebo on functional outcomes and safety in subjects dosed 18 to 36 hours after suffering a moderate to moderately-severe acute, ischemic stroke.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of MultiStem on functional outcome in subjects with ischemic stroke.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the efficacy of MultiStem on functional, neurological, mortality, secondary infection, and hospitalization outcomes in subjects with ischemic stroke; and
- To evaluate the safety of MultiStem in subjects with ischemic stroke.

2.3 Tertiary Objectives

The tertiary objectives of this study are the following:

- To evaluate the impact of MultiStem on quality of life and healthcare and rehabilitation services utilization in subjects with ischemic stroke; and
- To evaluate the mechanism of action of MultiStem through blood biomarkers, and spleen and brain imaging outcomes in subjects with ischemic stroke.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a pivotal Phase 3, randomized, double-blind, placebo-controlled, multicenter international study. The total study duration for safety follow-up will be 12 months. Approximately 300 subjects who have experienced an acute cortical ischemic stroke and fulfill all the eligibility criteria will be enrolled into the study in approximately 50 to 60 sites globally.

Approximately 300 subjects will be randomized in a 1:1 ratio (MultiStem [n=150] or placebo [n=150]) to receive a single IV infusion of 1.2 billion cells of MultiStem. Randomization will be stratified by Baseline NIHSS score (≤12 and ≥13), concomitant reperfusion therapy (Yes or No), and age (18 to 64 and ≥65 years). All subjects will be enrolled continuously into the study. Enrollment of subjects receiving concomitant reperfusion therapy (tPA, mechanical reperfusion [MR], or tPA + MR) will be limited to 40% of the entire randomized study population (approximately 120 subjects) with the tPA + MR sub-group being limited to 10% of the entire randomized study population.

Protocol stopping rules will be in place, with an independent Data Safety Monitoring Board (DSMB) assembled if serious safety events, including infusion reactions, occur related to investigational product. In addition, the DSMB will meet during the subject enrollment period to examine the unblinded safety data.

Subjects will be evaluated at Baseline, prior to infusion and post-infusion, 24 hours from the start of the infusion, 48 hours from the start of the infusion, Day 7, Day 30, Day 90, Day 180, and Day 365, or at the Early Termination (ET) Visit. To prevent subjects from being lost to follow-up, study sites will contact subjects every other month (Day 60, Day 150, Day 210, Day 270, and Day 330 [±7 days]) remotely to update the subject's medical status and disposition.

At the Screening Visit, subjects or legally authorized representatives (LARs) will provide written informed consent and undergo standard of care procedures, evaluation for inclusion/exclusion criteria, medical history, a physical examination, height and weight, pulse oximetry, concomitant medication assessments, 12-lead electrocardiogram (ECG), blood safety laboratory assessments, pregnancy testing, vital sign assessments, NIHSS assessment, pre-stroke mRS historical assessment, and brain magnetic resonance imaging (MRI)/computed tomography (CT).

The Screening Barthel Index score can be collected any time prior to the start of the infusion.

At the Baseline Visit (Day 0), subjects will be re-evaluated for inclusion/exclusion criteria, undergo a physical examination, vital signs, pulse oximetry, adverse event (collection begins from the start of the infusion) and concomitant medication assessments, blood safety laboratory collection, allogeneic antibody and exploratory blood biomarker collections, and a NIHSS assessment.

Subjects meeting eligibility requirements will be randomized and receive an IV infusion of MultiStem or placebo (18 to 36 hours post-stroke).

During the study, assessments of safety will include the evaluation of adverse events and concomitant medications, clinical laboratory results, allogeneic antibody testing, vital signs, pulse oximetry, 12-lead ECGs, and physical examinations. Efficacy will be assessed by mRS, NIHSS, Barthel Index, and EuroQol 5 dimensions (EQ-5D) scores. Healthcare and rehabilitation services

utilization will be assessed during the study. Exploratory blood biomarkers will be assessed at Baseline and during the study.

Subjects at selected sites will undergo ultrasound of the spleen and brain MRI (diffusion tensor imaging [DTI]) at Baseline (prior to the start of the infusion) and throughout the study to explore the mechanism of action of MultiStem.

3.2 Study Indication

MultiStem is an allogeneic, RMAT indicated for treatment of acute ischemic stroke within 36 hours after symptom onset.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects will be eligible for the study if they meet all of the following inclusion criteria:

1. Male or female subjects 18 years of age or older;
2. Clinical diagnosis of ischemic stroke involving cerebral cortex;
   - This inclusion criterion requires clinical signs that are consistent with imaging abnormalities required under inclusion criterion #5. Clinical diagnosis is defined as rapidly developed clinical signs of 1 or more focal (and potentially accompanying global) persistent disturbance(s) of cerebral function, with no apparent cause other than arterial occlusive ischemic stroke that involves cerebral cortex;
3. Onset of stroke symptoms must have occurred 18 to 36 hours prior to the planned start of administration of the investigational product;

   Note: Time of onset is defined as the time point, if known, when symptoms first began. For a stroke that occurred during sleep, or in an individual unable to report the time that symptoms began, the time of onset is defined as the time point when the subject was last observed to exhibit normal neurological function or was self-reported to have normal function;
4. Occurrence of a moderate to moderately severe stroke with a persistent neurologic deficit documented by a NIHSS score of 8 to 20 (inclusive) that does not change by ≥4 points from the Screening to the Baseline assessment;

   Note: The Screening NIHSS score used for determination of eligibility should be collected as soon as possible following admission to the hospital. In the event a subject receives concomitant reperfusion therapy the subject's Screening NIHSS score is encouraged to be collected prior to any concomitant reperfusion therapy but can be collected as late as 4 hours following completion of the last reperfusion (mechanical or pharmacologic) therapy;
5. Confirmation of hemispheric cortical infarct by brain MRI or CT demonstrating an acute ischemic infarct measuring ≥5 mL and ≤100 mL;
6. A mRS score of 0 or 1 prior to the onset of symptoms of the current stroke, by either self-reported history or by family/caregiver report;
7. Female subjects must not be pregnant, breastfeeding, or planning on becoming pregnant during the study; and either:
   a. Not of childbearing potential, defined as one who has been postmenopausal for at least 1 year, or has been surgically sterilized; or
   b. Agree to use a medically accepted, effective method of avoiding pregnancy through the Day 90 Visit. Effective methods of contraception are defined as those that result in a low failure rate (<1% per year) when used consistently and correctly. Such methods include the use of oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products (such as an intrauterine diaphragm, condoms, or spermicides);

8. Male subjects with female sexual partners of childbearing potential must also agree to use an effective method of avoiding pregnancy through the Day 90 Visit;
9. Subjects or legally authorized representatives must freely sign the informed consent form (ICF) after the nature of the study and the disclosure of his/her data have been explained;
10. Willing and able to comply with all aspects of the treatment and testing schedule; and
11. Willing and able to return to the study site for the post-treatment evaluations.

4.2 Exclusion Criteria

Subjects will not be eligible for the study if they meet any of the following exclusion criteria:

1. Presence of a lacunar or a brainstem infarct on MRI or CT as the etiology of current stroke symptoms;
2. Coma (score of 3 for item 1a of NIHSS);
3. Occurrence of a hemorrhagic transformation of ischemic stroke as evidenced by brain MRI or CT that is clinically significant in the opinion of the Investigator;
4. Fluctuation in neurologic status since the onset of stroke suggesting possible progression or expansion of stroke, transient ischemic attack, or stroke mimic;
5. Onset of stroke >28 hours prior to the start of Screening;

   Note: Onset of stroke >28 hours prior to the start of Screening would not allow for administration of investigational product per protocol;
6. Less than 6 hours between the Screening and Baseline NIHSS assessment;
7. Initiation of IV tPA infusion >4.5 hours and/or MR (defined as time of groin puncture) >8 hours after the onset of stroke;

   Note: tPA implies not only recombinant human tissue plasminogen activator, but also its engineered derivatives, including tenecteplase, Retavase®, and potentially other such agents that might conceivably reach the market (once they are approved and including desmoteplase, lanoteplase, etc.);
8. Plan to have a neurovascular procedure (e.g., carotid endarterectomy, stent placement, etc.) within the first year following stroke;
9. Pre-existing ipsilateral focal neurologic deficits that would complicate evaluation;
10. Seizure since the onset of stroke or prior history of seizures, with the exception of simple febrile seizures in childhood;
11. Major neurologic event such as stroke or clinically significant head trauma in the 6 months preceding study entry;
12. Uncontrolled hypertension prior to randomization, defined as persistent systolic blood pressure >220 mmHg or diastolic blood pressure >120 mmHg despite antihypertensive therapy;
13. Blood glucose level <50 mg/dL or >350 mg/dL prior to randomization despite concomitant therapy;

14. Significant comorbid medical condition(s), including, but not limited to:
    a. End-stage renal disease requiring renal replacement therapy;
    b. Advanced liver disease (e.g., Childs-Pugh score >10);
    c. Severe congestive heart failure (e.g., New York Heart Association score of III or IV) or ejection fraction <30%;
    d. Severe lung disease requiring continuous home oxygen; or
    e. Symptomatic refractory angina requiring daily treatment with nitrates or other medications;
15. Concurrent systemic infection or severe local infection;
16. Immunocompromised state due to immunosuppressive medications or as evidenced by hematologic studies or history of opportunistic infection;
17. History of Alzheimer's disease or other dementias, Parkinson's disease, or any other neurological disorder that in the opinion of the Investigator would affect the subject's ability to participate in the study or confound study assessments;
18. History of malignancy of any type within 2 years of stroke onset, with the exception of adequately treated basal or squamous cell carcinoma of the skin;
19. Life expectancy less than 90 days;
20. Prior surgical removal of the spleen or functional asplenia;
21. Allergy or religious objections to human tissue or bovine or porcine products;
22. Participation in any other study involving an investigational product or device within the last 30 days or planned participation in investigational rehabilitation stroke recovery program; or
23. Other serious medical or psychiatric illness that is not adequately controlled and, in the Investigator's opinion, would not permit the subject to be managed or evaluated according to the protocol.

4.3 Withdrawal Criteria

Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- The subject or LAR withdraws consent or requests discontinuation from the study for any reason; or
- Termination of the study by the Sponsor or the regulatory authority.

If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the ET Visit (Day 365/ET). The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

Every effort should be made to minimize the number of subjects for whom follow-up data are not collected as missing data can adversely affect the validity or interpretation of the study results.

Withdrawn subjects will not be replaced.

4.3.1 Lost to Follow-up

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records. A file will be considered closed after the site completes 3 phone calls followed by a certified letter to the last known address of the subject with no response obtained.

Every effort should be made to minimize the number of subjects for whom follow-up data are not collected as missing data can adversely affect the validity or interpretation of the study results.

Every effort will be made by the Investigator to contact the subject before the subject is declared lost to follow-up. This level of diligence is necessary to obtain (at a minimum) vital status (whether the subject is alive) and thus avoid lost to follow-up for efficacy and safety assessment. All sites will receive training on how vital status may be collected and monitored in accordance with local/legal practices and ethical regulations for all subjects randomized, including those who did not receive investigational product.

If vital status is determined, the subject will not be considered lost to follow-up.

4.4 Enrollment Stopping Rules

An independent DSMB will meet after approximately one-third and approximately two-thirds of the subject enrollment are complete to examine unblinded safety data. See Section 9.2.4 for details about the DSMB. The stopping rules for the study include any of the following until the DSMB determines if it is safe for the study to continue enrollment:

- Serious adverse event (SAE) assessed through 3 days post-infusion that is related to investigational product; and/or
- Any Grade 3 or 4 infusion-related reaction (Common Terminology Criteria for Adverse Events v4.0) in the first 24 hours post-infusion (see Appendix B for definitions and management of Grade 2 and 4 infusion-related reactions).

5 STUDY TREATMENTS

5.1 Treatment Groups

Subjects will be randomly assigned to receive a single IV infusion of MultiStem or matching placebo at Baseline (Day 0 [18 to 36 hours post-stroke]). MultiStem will be provided in a 1.2 billion cell dose ±20%.

5.2 Rationale for Dosing

A comprehensive non-clinical toxicology and safety program of GLP and non-GLP studies has been conducted with MultiStem. The results of these studies demonstrated no effects of MultiStem on pulmonary function, cardiovascular safety parameters, or chemistry and hematology parameters along with no evidence of cell-mediated immunogenicity or tumorigenicity with MultiStem use. In addition, standard drugs used to treat ischemic stroke do not affect MultiStem cell viability and function.

The highest single doses studied in these aforementioned non-clinical studies were 40 million MultiStem cells/dose (200 million cells/kg) in rats or 10 million MultiStem cells/dose (500 million cells/kg) in mice. This animal data provides up to an approximate 13-fold safety margin on a per kilogram weight basis over the highest anticipated individual IV dose to be administered in the proposed Phase 3 ischemic stroke clinical study (1.2 billion total cells or 15 million cells/kg/dose based on an 80 kg person). No maximum tolerated dose has yet been established in non-clinical studies, as all doses examined to date have exhibited good safety and tolerability.

5.3 Randomization and Blinding

Each subject who satisfies the eligibility criteria and is accepted for the study will be assigned a unique identification number. The Investigator or designee must contact the Medpace ClinTrak® Interactive Response Technology (CTIRT) to acquire the unique identification number for each subject. Subject numbers will consist of 6 digits. The first 3 digits will reflect the site number assigned to the Investigator, followed by a 3-digit subject number.

The subject number will be used to identify the subject throughout the study and will be entered on all study documents.

A subject number will not be assigned to more than 1 subject. If a subject is not eligible to receive treatment or if the subject discontinues from the study, the subject number cannot be reassigned to another subject.

Once the subject identification number has been assigned, a confirmation e-mail will be sent to all site personnel.

Approximately 300 subjects will be randomly assigned to receive either MultiStem or placebo in a 1:1 ratio (MultiStem [n=150] or placebo [n=150]). Randomization will be stratified by Baseline NIHSS score (≤12 and ≥13), concomitant reperfusion therapy (Yes or No), and age (18 to 64 and ≥65 years). All subjects will be enrolled continuously into the study. Enrollment of subjects receiving concomitant reperfusion therapy (tPA, MR, or tPA + MR) will be limited to 40% of the entire randomized study population (approximately 120 subjects) with the tPA + MR sub-group

being limited to 10% of the entire randomized study population. The investigational product label will indicate the study number, but will not indicate the treatment assignment.

At each site, designated staff at a pharmacy or equivalent facility will be unblinded to subject treatment assignments. All investigational product will be prepared and dispensed by the designated unblinded site personnel. The designated site personnel must contact the Medpace CTIRT to acquire the treatment assignment. Treatment assignments for the individual subjects will be determined through a computer generated randomization list prepared by Medpace and accessed using the Medpace CTIRT system. Instructions for access and use of the Medpace CTIRT system are provided in the study manual.

Randomization to treatment using Medpace CTIRT must occur prior to preparation of investigational product by the designated unblinded site personnel. A site blinding plan will be discussed, reviewed, and signed by both the blinded Investigator and the lead unblinded site personnel prior to site initiation. This will define blinded versus unblinded roles and responsibilities at the site and ensure study blinding is maintained. Unblinded site personnel who will store and prepare investigational product will also complete training and follow Standard Operating Procedures provided by the Sponsor for preparation and blinding of investigational product for each randomized subjects' IV infusion.

The Investigator or designee must contact the Medpace CTIRT to report subjects who are not randomized due to eligibility requirements.

5.4 Breaking the Blind

In an emergency, when knowledge of the subject's treatment assignment is essential for the clinical management or welfare of the subject, the Investigator should unblind the treatment assignment. It is encouraged that the Investigator make every effort to contact the Medpace Medical Monitor before proceeding with the unblinding process, but it is not required.

Prior to unblinding the subject's treatment assignment, the Investigator should assess the relationship of an adverse event to the administration of the investigational product (definitely, probably, possibly, unlikely, unrelated). The Investigator must then contact Medpace CTIRT to unblind an individual subject's treatment assignment. The Investigator must record the date and reason for breaking the blind on the appropriate eCRF and source documents.

Although the designated unblinded personnel preparing the investigational product at the study site will be unblinded, the treatment assignment will not be provided to other site personnel, including the Investigator, at any time during the conduct of the study, except in the case of a true emergency, as described above.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

MultiStem will be provided to the clinical sites in units of 1.2 billion cells ±20%. Other components are PlasmaLyte-A, dimethyl sulfoxide, and human serum albumin.

The matching placebo contains PlasmaLyte-A, dimethyl sulfoxide, and human serum albumin.

5.5.2 Investigational Product Preparation and Dispensing

Investigational product will be provided to the pharmacy or equivalent facility in a frozen state and should be stored under appropriate conditions. Prior to use, the investigational product will be thawed, prepared, and blinded for infusion by appropriate unblinded site personnel following the instructions provided and delivered to the clinical site for administration.

5.5.3 Investigational Product Administration

Subjects will receive a single IV infusion of MultiStem or matching placebo at Baseline (Day 0 [18 to 36 hours post-stroke]).

5.5.4 Treatment Compliance

All investigational product will be prepared and dispensed by the designated site personnel. Subjects will receive a single IV infusion of MultiStem or matching placebo.

5.5.5 Storage and Accountability

Investigational product must be stored in a locked and secure storage facility, accessible only to those individuals authorized by the Investigator or Athersys, Inc. to process and dispense the investigational product. The unblinded staff designees at the pharmacy or equivalent facility will keep accurate records on a form provided by Medpace of all investigational products received and dispensed. At the conclusion of the study, the unblinded clinical research associate (CRA) will account for all used and unused investigational product. All unused investigational product will be returned to Athersys, Inc. according to instructions provided. The Investigator agrees not to distribute investigational product to any person except those named on the Food and Drug Administration (FDA) 1572 form and subjects participating in the study.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The following medications and procedures are prohibited:

- Subjects must not have taken any investigational agent or device within 30 days prior to Screening;
- Subjects cannot participate in any other investigational medication study while participating in this study;
- Subjects cannot have received tPA >4.5 hours and/or MR (defined as time of groin puncture) >8 hours after the onset of stroke; and/or

  Note: tPA implies not only recombinant human tissue plasminogen activator, but also its engineered derivatives, including tenecteplase, Retavase®, and potentially other such agents

that might conceivably reach the market (once they are approved and including; desmoteplase, lanoteplase, etc.);

- Subjects cannot, at the time of enrollment, have plans to have a neurovascular procedure (e.g., carotid endarterectomy, stent placement, etc.) within the first year following stroke.

5.6.2 Documentation of Prior and Concomitant Medication Use

Any medications administered from the time of hospital admission through the Day 90 Visit must be documented on the Concomitant Medication eCRF. In addition, concomitant medication use associated with SAEs will be collected through Day 365.

6 STUDY PROCEDURES

A detailed schedule of procedures for each study cohort is provided in Appendix A, Table 3.

6.1 Informed Consent

Written informed consent for the study will be obtained from all subjects or LARs before any protocol specific procedures are carried out, with the exception of standard of care procedures. Standard of care procedures may be performed prior to written informed consent. See Section 11.3 for details on informed consent.

6.2 Screening Visit (0 to 28 Hours Post-Stroke)

Screening procedures can potentially be performed as part of standard of care procedures.

The following procedures will be performed at Screening:

- Obtain signed informed consent;
- Obtain medical history;
- Record demographics;
- Record height and weight;
- Perform urine or serum pregnancy test on female subjects of childbearing potential;
- Perform a physical examination;
- Perform a 12-lead ECG;
- Obtain vital signs (including blood pressure, pulse, respiratory rate, and temperature);
- Perform pulse oximetry;
- Obtain blood samples for chemistry and hematology testing (local laboratory);
- Record concomitant medications;
- Determine NIHSS score;
    - Note: The Screening NIHSS score used for determination of eligibility should be collected as soon as possible following admission to the hospital. In the event a subject receives concomitant reperfusion therapy the subject's Screening NIHSS score is encouraged to be collected prior to any concomitant reperfusion therapy but can be collected as late as 4 hours following completion of the last reperfusion (mechanical or pharmacologic) therapy;
    - Note: There should be ≥6 hours between the Screening and Baseline NIHSS assessment;
- Determine mRS score based on historical values prior to the onset of symptoms of the current stroke by either self-reported history or family/caregiver report;
- Determine Barthel Index score based on historical values prior to the onset of symptoms of the current stroke by either self-reported history or family/caregiver report;
    - Note: The Screening Barthel Index score can be collected any time prior to the start of the infusion;

- Perform brain MRI/CT;
- For subjects in the sub-study only: perform a brain MRI-DTI any time prior to the start of the infusion; and
- If the subject is a screen failure, a blinded team member should contact Medpace CTIRT to register the subject as a pre-randomization failure.

6.3 Baseline Visit (Day 0)

The following procedures will be performed at the Baseline Visit (Day 0) before the start of the infusion:

- Evaluate inclusion/exclusion criteria;
- Perform a physical examination;
- Obtain vital signs just prior to infusion start, but no more than 60 minutes prior;
- Perform pulse oximetry just prior to infusion start, but no more than 60 minutes prior;
- Obtain blood samples for chemistry and hematology testing (central laboratory);
- Obtain blood sample for allogeneic antibody testing;
- Obtain blood sample for exploratory blood biomarkers;
- Determine NIHSS score 18 to 34 hours from the time of stroke onset (final eligibility assessment);
    - Note: There should be ≥6 hours between the Baseline and Screening NIHSS assessment;
    - Note: The Baseline NIHSS score should not have changed by ≥4 points from the Screening NIHSS. The Baseline NIHSS score should be confirmed prior to randomization;
- For subjects in the sub-study only: perform a spleen ultrasound;
- For subjects in the sub-study only: perform a brain MRI-DTI once any time prior to the start of the infusion;
- Blinded team member to randomize patient, then an unblinded team member should contact Medpace CTIRT to acquire treatment group assignment; and
- Record concomitant medications.

Infusion:

- Perform infusion of investigational product.
    - Note: Infusion should start 18 to 36 hours from the onset of stroke.

The following procedures will be performed at the Baseline Visit (Day 0) after the start of the infusion (18 to 36 hours post-stroke):

- Obtain vital signs every 30 (±5) minutes for the first 2 hours after the infusion start and then at 4 hours (±30 minutes) and 6 hours (±30 minutes) after the infusion start;
- Perform pulse oximetry every 30 (±5) minutes for the first 2 hours after the infusion start and then at 4 hours (±30 minutes) and 6 hours (±30 minutes) after the infusion start; and
- Assess adverse events and record concomitant medications.

6.4 Post-Infusion Visits – 24 Hours From the Start of the Infusion Through Day 365

Following infusion of investigational product, subjects will be monitored, visits/procedures will be completed in the hospital until discharge, and then subjects will return for outpatient visits/procedures according to the schedule outlined below.

Note: If hospital discharge occurs before the Day 7 window, Day 7 procedures can be performed in the hospital at discharge.

Note: The post-infusion visits may be conducted remotely if the subject is unable to attend the site visit. It is preferable to perform a remote visit rather than have the subject miss the visit; the possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance.

6.4.1 24 Hours From the Start of the Infusion (±6 Hours)

The following procedures will be performed at 24 hours from the start of the infusion:

- Perform a physical examination;
- Perform a 12-lead ECG;
- Obtain vital signs;
- Perform pulse oximetry;
- For subjects in the sub-study only: perform a spleen ultrasound;
- Obtain blood sample for chemistry and hematology testing (central laboratory); and
- Assess adverse events and record concomitant medications.

6.4.2 48 Hours From the Start of the Infusion (±6 Hours)

The following procedures will be performed at 48 hours from the start of the infusion:

- Perform a 12-lead ECG;
- Obtain vital signs;
- Perform pulse oximetry;
- For subjects in the sub-study only: perform a spleen ultrasound;
- Obtain blood sample for chemistry and hematology testing (central laboratory);

- Obtain blood sample for exploratory blood biomarkers; and
- Assess adverse events and record concomitant medications.

6.4.3 Day 7 (±2 Days)/Day of Discharge

The following procedures will be performed at Day 7:

- Obtain vital signs;
- Perform pulse oximetry;
- For subjects in the sub-study only: perform a spleen ultrasound;
- Obtain blood sample for chemistry and hematology testing (central laboratory);
- Obtain blood sample for exploratory blood biomarkers;
- Determine NIHSS score;
  - Note: NIHSS assessments are preferred to be completed in a face-to-face setting. If conducted remotely, telemedicine is acceptable, and telephone is not acceptable. NIHSS assessments for post-Baseline visits must be completed by staff who are certified in NIHSS administration. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine mRS score;
  - Note: The mRS assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. When evaluating subjects to determine the mRS score, the raters of the score must not make any attempt to exclude or correct for disability that the rater attributes to causes other than stroke. The score should be recorded without regard to the cause of the disabilities that impact the score or the time point at which the disabilities occurred. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine Barthel Index score;
  - Note: Barthel Index assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Record the date the subject has been admitted to and/or discharged from the ICU, the hospital, and to a non-hospital residential care facility following the initial stroke;

- Inquire about rehabilitation activities (e.g., inpatient physical therapy, outpatient physical therapy, etc.); and
- Assess adverse events and record concomitant medications.

6.4.4 Day 30 (±3 Days)

The following procedures will be performed at Day 30:

- Perform a physical examination;
- Obtain blood sample for chemistry and hematology testing (central laboratory);
- Obtain blood sample for allogeneic antibody testing;
- Determine NIHSS score;
  - Note: NIHSS assessments are preferred to be completed in a face-to-face setting. If conducted remotely, telemedicine is acceptable, and telephone is not acceptable. NIHSS assessments for post-Baseline visits must be completed by staff who are certified in NIHSS administration. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine mRS score;
  - Note: mRS assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. When evaluating subjects to determine the mRS score, the raters of the score must not make any attempt to exclude or correct for disability that the rater attributes to causes other than stroke. The score should be recorded without regard to the cause of the disabilities that impact the score or the time point at which the disabilities occurred. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine Barthel Index score;
  - Note: Barthel Index assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Record the date the subject has been admitted to and/or discharged from the ICU, the hospital, and to a non-hospital residential care facility following the initial stroke;
- Inquire about rehabilitation activities (e.g., inpatient physical therapy, outpatient physical therapy, etc.); and

- Assess adverse events and record concomitant medications.

6.4.5 Day 60 (±7 Days) Remote Visit

Study sites will contact the subject remotely to perform the following procedures at Day 60:

- Record the date the subject has been admitted to and/or discharged from the ICU, the hospital, and to a non-hospital residential care facility following the initial stroke;
- Inquire about rehabilitation activities (e.g., inpatient physical therapy, outpatient physical therapy, etc.); and
- Assess adverse events and record concomitant medications.

6.4.6 Day 90 (±7 Days)

The following procedures will be performed at Day 90:

- Determine NIHSS score;
  - Note: NIHSS assessments are preferred to be completed in a face-to-face setting. If conducted remotely, telemedicine is acceptable, and telephone is not acceptable. NIHSS assessments for post-Baseline visits must be completed by staff who are certified in NIHSS administration. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine mRS score;
  - Note: mRS assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. When evaluating subjects to determine the mRS score, the raters of the score must not make any attempt to exclude or correct for disability that the rater attributes to causes other than stroke. The score should be recorded without regard to the cause of the disabilities that impact the score or the time point at which the disabilities occurred. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine Barthel Index score;
  - Note: Barthel Index assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Record the date the subject was admitted to and/or discharged from the ICU, the hospital, and to a non-hospital residential care facility following the initial stroke;

- For subjects in the sub-study only: perform a brain MRI-DTI;
- Measure health-related quality of life with the EQ-5D questionnaire;
- Inquire about rehabilitation activities (e.g., inpatient physical therapy, outpatient physical therapy, etc.); and
- Assess adverse events and record concomitant medications.

6.4.7 Day 150, Day 210, Day 270, and Day 330 (±7 Days) Remote Visits

Study sites will contact the subject remotely to perform the following procedures at Day 150, Day 210, Day 270, and Day 330:

- Record the date the subject was admitted to and/or discharged from the ICU, the hospital, and to a non-hospital residential care facility following the initial stroke;
- Inquire about rehabilitation activities (e.g., inpatient physical therapy, outpatient physical therapy, etc.); and
- Assess adverse events.

6.4.8 Day 180 (±7 Days)

The following procedures will be performed at Day 180:

- Determine NIHSS score;
  - Note: NIHSS assessments are preferred to be completed in a face-to-face setting. If conducted remotely, telemedicine is acceptable, and telephone is not acceptable. NIHSS assessments for post-Baseline visits must be completed by staff who are certified in NIHSS administration. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine mRS score;
  - Note: mRS assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. When evaluating subjects to determine the mRS score, the raters of the score must not make any attempt to exclude or correct for disability that the rater attributes to causes other than stroke. The score should be recorded without regard to the cause of the disabilities that impact the score or the time point at which the disabilities occurred. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine Barthel Index score;
  - Note: Barthel Index assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not

possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;

- Record the date the subject was admitted to and/or discharged from the ICU, the hospital, and to a non-hospital residential care facility following the initial stroke;
- Inquire about rehabilitation activities (e.g., inpatient physical therapy, outpatient physical therapy, etc.); and
- Assess adverse events.

6.5 Day 365 (±7 Days)/Early Termination Visit and Withdrawal Procedures

The end of treatment for subjects completing the study is Day 365. For subjects who are withdrawn from the study prior to completion, all Day 365 procedures will be performed at the ET Visit.

Note: The post-infusion visits may be conducted remotely if the subject is unable to attend the site visit. It is preferable to perform a remote visit rather than have the subject miss the visit; the possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance.

The procedures to be conducted at Day 365/ET include the following:

- Perform a physical examination;
- Obtain vital signs;
- Perform pulse oximetry;
- Determine NIHSS score;
    - Note: NIHSS assessments are preferred to be completed in a face-to-face setting. If conducted remotely, telemedicine is acceptable, and telephone is not acceptable. NIHSS assessments for post-Baseline visits must be completed by staff who are certified in NIHSS administration. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- Determine mRS score;
    - Note: mRS assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. When evaluating subjects to determine the mRS score, the raters of the score must not make any attempt to exclude or correct for disability that the rater attributes to causes other than stroke. The score should be recorded without regard to the cause of the disabilities that impact the score or the time point at which the disabilities occurred. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;

- Determine Barthel Index score;
  - Note: Barthel Index assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance;
- For subjects in the sub-study only: perform a brain MRI-DTI;
- Measure health-related quality of life with the EQ-5D questionnaire;
- Record the date the subject was admitted to and/or discharged from the ICU, the hospital, and to a non-hospital residential care facility following the initial stroke;
- Inquire about rehabilitation activities (e.g., inpatient physical therapy, outpatient physical therapy, etc.);
- Inquire about occupational status (e.g., employed or retired, full or part-time status, etc.);
- Assess adverse events; and
- Record concomitant medications if the ET Visit occurs on or prior to Day 90 (ET Visit only).

7 EFFICACY ASSESSMENTS

7.1 Endpoints

7.1.1 Primary Efficacy Variable

The primary efficacy variable is the mRS score at Day 90. Differences between the MultiStem and placebo treatment groups in the distribution of Day 90 mRS scores will be evaluated by shift analysis.

7.1.2 Secondary Efficacy Variables

The key secondary efficacy variables are defined below. Differences between the MultiStem and placebo treatment groups will be evaluated using hierarchical testing.

- Proportion of subjects achieving an excellent outcome at Day 365 defined by all of the following criteria: mRS score of ≤1, NIHSS total score of ≤1, and Barthel Index score of ≥95;
- Proportion of subjects achieving an excellent outcome at Day 90 defined by all of the following criteria: mRS score of ≤1, NIHSS total score of ≤1, and Barthel Index score of ≥95; and
- Proportion of subjects with a mRS score of ≤2 at Day 90.

Other secondary efficacy variables will examine the difference between the MultiStem and placebo treatment groups for the following:

- Global disability throughout the range of mRS scores by shift analysis at Day 365;
- Proportion of subjects with a Barthel Index score of ≥95 at Day 90 and Day 365;
- Proportion of subjects with a NIHSS score of ≤1 at Day 90 and Day 365;
- Proportion of subjects with a mRS score of ≤1 at Day 90 and Day 365;
- Number of hospital-free days through Day 28;
- Number of ICU-free days through Day 28;
- Number of hospital-free days through Day 90;
- Number of hospital and non-hospital residential care-free days through Day 90;
- Proportion of subjects with all-cause mortality through Day 90;
- Proportion of subjects with secondary infections through Day 90;
- Proportion of subjects with urinary tract infections through Day 90; and
- Proportion of subjects who survived without life-threatening adverse events at Day 90.

7.1.3 Tertiary Efficacy Variables

Tertiary efficacy variables include the difference between the MultiStem and placebo treatment groups for the following:

- Changes in blood biomarkers (white blood cell populations and inflammatory markers) from Baseline to 48 hours from the start of the infusion and Day 7;
- Quality of life measured by the EQ-5D questionnaire at Day 90 and Day 365;
- Number of hospital and non-hospital residential care-free days through Day 365;
- Rehabilitation services utilization through Day 365;
- Changes in spleen size via exploratory imaging from Baseline to 24 hours from the start of the infusion, 48 hours from the start of the infusion and Day 7/discharge (sub-study at selected sites only); and
- Changes in white matter tract organization via exploratory imaging from Baseline to Day 90 and Day 365 (sub-study at selected sites only).

7.2 Assessments

7.2.1 National Institutes of Health Stroke Scale

The NIHSS assessment is a standardized method that uses a 42-point scale to measure the level of impairment caused by a stroke. The 42-point scale measures several aspects of brain function, including consciousness, vision, sensation, movement, speech, and language (0 = no stroke and 42 = severe stroke). Determination of NIHSS score will be performed at Screening (0 to 28 hours post-stroke), Baseline (Day 0 [18 to 34 hours post-stroke] before infusion start), Day 7, Day 30, Day 90, Day 180, and Day 365/ET.

The Screening NIHSS score used for determination of eligibility should be collected as soon as possible following admission to the hospital. In the event a subject receives concomitant reperfusion therapy the subject's Screening NIHSS score is encouraged to be collected prior to any concomitant reperfusion therapy but can be collected as late as 4 hours following completion of the last reperfusion (mechanical or pharmacologic) therapy. The Baseline NIHSS assessment should occur between 18 and 34 hours from the time of stroke onset and ≥6 hours after the last NIHSS assessment at Screening. The Baseline NIHSS score should not have changed by ≥4 points from the Screening NIHSS. The Baseline NIHSS score should be confirmed prior to randomization.

NIHSS assessments are preferred to be completed in a face-to-face setting. If conducted remotely, telemedicine is acceptable, and telephone is not acceptable. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance.

NIHSS assessments for post-Baseline visits must be completed by staff who are certified in NIHSS administration. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible.

7.2.2 Modified Rankin Scale

The mRS measures independence rather than performance of specific tasks. The mRS is not a patient-reported outcome, but should be administered by appropriate clinical site personnel based on the full exploration of the subject's current functional status at the time of the interview. This tool incorporates mental as well as physical adaptations to the neurological deficits. The scale consists of 7 grades, from 0 to 6, with 0 corresponding to no symptoms and 6 corresponding to death. Training for mRS administration will be provided along with guidance in the study manual.

Note: In exception to the above description, the premorbid mRS score determined at Screening **is** based on historical values prior to the onset of symptoms of the current stroke by either self-reported history or family/caregiver report while scores at subsequent visits are based on values obtained following the onset of the current stroke.

Assessments of the mRS score will be performed at Screening (0 to 28 hours post-stroke [prior to the onset of symptoms of the current stroke by either self-reported history or family/caregiver report]) for historical pre-stroke inclusion criterion and then at Day 7, Day 30, Day 90, Day 180, and Day 365/ET for efficacy.

Note: The mRS assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance. When evaluating subjects to determine the mRS score, the raters of the score must not make any attempt to exclude or correct for disability that the rater attributes to causes other than stroke. The score should be recorded without regard to the cause of the disabilities that impact the score or time point at which the disabilities occurred.

7.2.3 Barthel Index

The Barthel Index is an instrument used to measure a subject's performance in 10 activities of daily life. The items can be divided into a group that is related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and a group related to mobility (ambulation, transfers, and stair climbing). The maximal score is 100 if 5-point increments are used, indicating the subject is fully independent in physical functioning. The lowest score is 0, representing a totally bedridden state. Assessments for Barthel Index score will be performed at Screening for historical pre-stroke inclusion criterion (0 to 28 hours post-stroke [prior to the onset of symptoms of the current stroke by either self-reported history or family/caregiver report]), Day 7, Day 30, Day 90, Day 180, and Day 365/ET. At Screening, the Barthel Index score can be collected any time prior to the start of the infusion.

Barthel Index assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance.

Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible.

7.2.4 EQ-5D Questionnaire

The EQ-5D questionnaire is a standardized instrument used to measure health outcome, specifically health-related quality of life in this study. The EQ-5D questionnaire will be administered at Day 90 and Day 365/ET.

7.2.5 Rehabilitation

Subjects will be asked about any rehabilitation activities that have taken place (e.g., inpatient physical therapy, outpatient physical therapy, etc.) at Day 7, Day 30, Day 60, Day 90, Day 150, Day 180, Day 210, Day 270, Day 330, and Day 365/ET.

7.2.6 Occupational Status

Questions about a subject's pre- and post-stroke occupational status (e.g., employed or retired, full or part-time status, etc.) will be asked at Day 365/ET.

7.2.7 Hospitalization

The date the subject has been admitted to and/or discharged from the ICU, hospital, and to a non-hospital residential care facility (such as in-patient rehabilitation, skilled nursing, or long-term acute care facility) should be recorded from the time of hospital admission to the clinical site following the initial stroke through Day 365.

For analysis, these data will be converted to ICU, hospital, and non-hospital residential care-free days to correct for the otherwise confounding effects of differential mortality on group hospital utilization data.

7.2.8 Exploratory Blood Marker Assessment

A blood sample for exploratory blood biomarker evaluation (white blood cell populations and inflammatory markers) will be drawn at Baseline (Day 0 before infusion start), 48 hours from the start of the infusion, and Day 7. For blood sampling procedures, including information on blood volume, collection tubes, sample processing, storage, and shipping, see the Laboratory Manual for this study.

7.2.9 Antibody Assessment

A blood sample for allogeneic antibody testing to MultiStem will also be drawn at Baseline (Day 0 before infusion start) and at Day 30.

7.2.10 Spleen Ultrasound (Sub-Study Only)

A spleen ultrasound will be performed for subjects in the sub-study at Baseline (Day 0 before infusion start), 24 hours from the start of the infusion, 48 hours from the start of the infusion, and Day 7/discharge to examine changes in spleen size via exploratory imaging.

7.2.11 Brain MRI-DTI (Sub-Study Only)

A brain MRI-DTI will be performed for subjects in the sub-study any time prior to the start of the infusion (considered Baseline), and then at Day 90 and Day 365/ET to examine changes in white matter tract organization via exploratory imaging.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

A secondary endpoint in this clinical study will be the frequency and severity of adverse events through Day 365.

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the start of the infusion at Day 0 until study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. Beginning at the start of the infusion at Day 0, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at Screening or Baseline should not be reported as an adverse event unless the medical condition or signs or symptoms present at Baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at Baseline and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For MultiStem the reference safety information is included in Section 6.3 of the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to investigational product using the categories of definitely, probably, possibly, unlikely, and unrelated.

8.1.3.1 Assessment of severity

- Mild – An event that is easily tolerated and generally not interfering with normal daily activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.
- Severe – An event that is incapacitating with inability to work or perform normal daily activities.

8.1.3.2 Causality assessment

The relationship of an adverse event to the administration of the investigational product is to be assessed according to the following definitions:

- Definitely related: Follows a reasonable temporal sequence from investigational product administration; abates upon discontinuation of the investigational product (dechallenge); and is confirmed by reappearance of the reaction on repeat exposure (rechallenge);
- Probably related: Follows a reasonable temporal sequence from investigational product administration, abates upon discontinuation of the investigational product (dechallenge), and cannot be reasonably explained by the known characteristics of the subject's clinical state;
- Possibly related: Follows a reasonable temporal sequence from investigational product administration and could have been produced by the subject's state or by other modes of therapy administered to the subject;
- Unlikely related: The temporal sequence between the adverse event and the investigational product administration is such that the drug is not likely to have had any reasonable association with the observed event and the adverse event could have been produced by the subject's clinical condition or by other modes of therapy administered to the subject; or
- Unrelated: The adverse event is definitely produced by the subject's clinical condition or by other modes of therapy administered to the subject and the adverse event does not follow a temporal sequence from investigational product administration.

The following factors should also be considered:

- The temporal sequence from investigational product administration-
  - The event should occur after the investigational product is given. The length of time from investigational product exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug-
  - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of investigational product-
  - Clinical and/or non-clinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the investigational product-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the investigational product should be considered.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
  - Note: An adverse event or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
  - Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or

situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
    - Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

8.3.1 Initial Reports

All SAEs occurring from the time of the start of the investigational product infusion at Day 0 until Day 365 must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria).

To report the SAE, complete the SAE form electronically in the Electronic Data Capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
E-mail: medpace-safetynotification@medpace.com

8.3.2 Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.3.3 Additional Reporting Requirements for Suspected Unexpected Serious Adverse Reaction

Athersys, Inc. is responsible for processing any suspected unexpected serious adverse reaction (SUSAR). The SUSARs are also referred to as alert reports, expedited safety reports, and investigational new drug safety reports.

A SUSAR is defined as any SAE that is determined to be associated with the use of study drug and is unexpected (not currently listed in the safety reference information [see the Investigator's Brochure] or is not listed at the specificity or severity that has been observed). Athersys, Inc. will notify all Investigators currently conducting MultiStem clinical studies of all SUSARs in accordance with applicable regulations. All SUSARs will be reported to the relevant regulatory authorities and IRBs/IECs according to the rules in effect in each country where study sites are located:

- If the SUSAR is fatal or life-threatening, regulatory authorities and ethics committees will be notified within 7 calendar days after Athersys, Inc. learns of the event.
- If the SUSAR is not fatal or life-threatening, regulatory authorities and ethics committees will be notified within 15 calendar days after Athersys, Inc. learns of the event.

These notifications will need to be filed in each site's study file and submitted to each site's IRB/IEC in accordance with policy.

Safety updates will be provided periodically to the regulatory authorities and IRBs/IECs responsible for the study according to the rules in effect in each country where study sites are located. These updates will include information on SUSARs and other relevant safety findings.

8.4 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA, applicable competent

authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

8.6 Medical and Surgical History

Medical history, including details regarding all illnesses and allergies, dates of onset, status of current condition, and smoking and alcohol use will be collected for all subjects at Screening (0 to 28 hours post-stroke). Additional information to be collected includes past surgical and medical procedures as well as medications.

8.7 Demographics

Demographic information including day, month, and year of birth (as permitted by country); race; and gender will be collected for all subjects at Screening (0 to 28 hours post-stroke).

8.8 Clinical Laboratory Evaluations

8.8.1 Standard Safety Laboratory Assessments

At Screening, a chemistry and hematology blood sample will be collected and analyzed at a local laboratory per the institutional requirements and local processes.

For the remainder of the study, starting at Day 0 (Baseline), chemistry and hematology blood samples will be collected and sent to a central laboratory.

Chemistry and hematology will be collected as marked in the Schedule of Procedures (Appendix A, Table 3). See the Laboratory Manual list of chemistry and hematology analytes.

Detailed procedures of sampling preparation, storage, and shipment will be described in a specific Laboratory Manual which will be provided to all sites.

The Investigator must review and sign all laboratory test reports. At Screening, subjects who have laboratory values that are outside the exclusionary limits specified in Section 4.2, may not proceed to randomization.

8.8.2 Pregnancy Test

A urine or serum pregnancy test (per standard of care) will be performed on female subjects of childbearing potential at Screening (0 to 28 hours post-stroke).

8.9 Vital Signs

Vital signs include blood pressure, pulse, respiratory rate, and temperature.

Vital signs will be collected at Screening (0 to 28 hours post-stroke), Baseline (Day 0) (pre- and post-infusion), 24 hours from the start of the infusion, 48 hours from the start of the infusion, Day 7, and Day 365/ET.

Note: Vital signs will be collected just prior to infusion start, but no more than 60 minutes prior; every 30 (±5) minutes for the first 2 hours after the infusion start; and then at 4 hours (±30 minutes) and 6 hours (±30 minutes) after the infusion start.

8.10 Pulse Oximetry

Oxygen saturation (via pulse oximetry) will be collected at Screening (0 to 28 hours post-stroke), Baseline (Day 0) (pre- and post-infusion), 24 hours from the start of the infusion, 48 hours from the start of the infusion, Day 7, and Day 365/ET.

Note: Oxygen saturation (via pulse oximetry) will be collected just prior to infusion start, but no more than 60 minutes prior; every 30 (±5) minutes for the first 2 hours after the infusion start; and then at 4 hours (±30 minutes) and 6 hours (±30 minutes) after the infusion start.

8.11 Electrocardiograms

A 12-lead ECG will be conducted at Screening (0 to 28 hours post-stroke), 24 hours from the start of the infusion, and 48 hours from the start of the infusion. Any clinically significant abnormalities will be captured as an adverse event.

8.12 Physical Examinations

A physical examination will be performed at Screening (0 to 28 hours post-stroke), Baseline (Day 0) (before infusion start), 24 hours from the start of the infusion, Day 30, and Day 365/ET.

The extent of the physical examination is at the discretion of the Investigator.

8.13 Height and Weight

Height will be collected at Screening. Height can be collected as the measured value or the reported value.

Weight will be collected at Screening.

9 STATISTICS

9.1 Analysis Populations

9.1.1 Intent-to-Treat Population

The Intent-to-Treat Population will include all randomized subjects. This population will be used for the primary and key secondary efficacy analyses.

9.1.2 Modified Intent-to-Treat Population/Safety Population

The Modified Intent-to-Treat Population will include all randomized subjects who receive study drug. Primary and key secondary efficacy analyses will be repeated using this population.

This population will also be used to summarize all safety data, and for safety analyses, will be referred to as the Safety Population.

9.1.3 Per Protocol Population

The Per Protocol Population will include all randomized subjects who do not have any violations or entry criteria or protocol deviations that could significantly impact the assessment or interpretation of efficacy data. Subject data will be reviewed by the clinical team to identify exclusions from the Per Protocol Population. The list of subjects to be excluded from the Per Protocol Population will be finalized prior to database unblinding.

9.2 Statistical Methods

A separate Statistical Analysis Plan will be prepared to provide additional details on the approach to analyses and data displays.

9.2.1 Analysis of Efficacy

9.2.1.1 Primary efficacy analysis

The primary efficacy variable will be the mRS score at Day 90. To compare the distributions of the mRS scores at Day 90, all mRS values (0 to 6) will be considered (except the categories 5 and 6 are collapsed into a single group). The proportion of subjects in each category will be summarized with counts and percentages and compared between the MultiStem group and placebo group. Specifically, the van Elteren test, an extension of the 2-sample Wilcoxon rank-sum test, stratified by Baseline NIHSS score (≤12 and ≥13), use of concomitant reperfusion therapy (Yes or No), and age group (18 to 64 years and ≥65 years) will be used for the primary comparison.

Furthermore, the probability that a randomly chosen subject who receives the MultiStem treatment will have a better mRS score than a randomly chosen subject from the same stratum receiving the placebo treatment, will be estimated. This measure does not depend on any parametric model assumption and was proposed by Howard et al.,[16] as the consistent companion of van Elteren test. Specifically, for each stratum, each subject from the MultiStem group will be paired with each subject from the placebo group in order to determine the percentage of subject pairs where the MultiStem subject achieved a better mRS score and the percentage where the placebo subject achieved a better mRS score. The stratum-specific percentages by their corresponding weighted averages (weighted by the stratum size) will be combined and the estimated probabilities that the mRS score from a MultiStem subject is better and worse than that from a placebo subject in the

same stratum will be reported. The difference of these 2 probabilities will be used to measure the treatment effect. The confidence interval of the difference will be constructed based on large sample approximations for the distribution of related U-statistics.

For the primary analysis, the last observation carried forward (LOCF) approach will be applied to impute missing data, e.g., a missing mRS score at Day 90 will be imputed by the last observed post-Baseline mRS score prior to Day 90. Subjects who die prior to Day 90 will have a mRS score of 6 imputed for the Day 90 analysis.

As a supportive analysis, an alternative measure for the treatment effect, the odds ratio (OR) from a stratified proportional odds model, will be estimated as well. The proportional odds model assumes a constant OR with respect to the dichotomized mRS score using cut-off values of 1, 2, 3, 4, and 5. The 95% confidence interval for the OR will be constructed. Furthermore, multivariate regression analysis will be performed to adjust for potential imbalances in important Baseline characteristics other than the selected stratification factors based on the stratified proportional odds model.

Sensitivity analyses will be performed in order to evaluate the impact of missing data on overall study conclusions.

9.2.1.2 Key secondary efficacy analyses

The key secondary variables will examine the difference between the MultiStem and placebo treatment groups using hierarchical testing for the following:

1. Proportion of subjects achieving an excellent outcome at Day 365 defined by all of the following criteria: mRS score of ≤1, NIHSS total score of ≤1, and Barthel Index score of ≥95;
2. Proportion of subjects achieving an excellent outcome at Day 90 defined by all of the following criteria: mRS score of ≤1, NIHSS total score of ≤1, and Barthel Index score of ≥95; and
3. Proportion of subjects with a mRS score of ≤2 at Day 90.

These key secondary endpoints will be compared between the randomized treatment groups with the overall Type I error controlled using hierarchical testing. Specifically, if statistical significance is observed on the primary effectiveness endpoint, the secondary clinical efficacy endpoints will then be tested in sequential fashion in the order presented, each at a level of 0.05, with testing ceasing once a null hypothesis cannot be rejected.

For each of the key secondary endpoints, the Cochran-Mantel-Haenszel test will be used, stratified by the stratification factors specified above. Treatment differences will be quantified using the difference in the proportion of having favorable outcome.

For each key secondary efficacy analysis, the LOCF approach will be applied to impute missing data. Subjects who die prior to the specified time point will have the worst possible outcome imputed for that analysis.

9.2.1.3 Other secondary and tertiary efficacy analysis

Other secondary efficacy endpoints, as well as tertiary endpoints, will be presented descriptively and analyzed with appropriate statistical methods. Specifically, the Cochran-Mantel-Haenszel test will be used for the dichotomized endpoints; the stratified Wilcoxon test (van Elteren test) will be

used for ordinal outcomes; and linear models will be used to analyze continuous outcomes. Where appropriate, models will be stratified by the stratification variables specified above.

9.2.2 Analysis of Safety

In general, safety analyses will be presented by treatment group and overall for the Safety Population.

9.2.2.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An overview of adverse events categories will be summarized with counts and percentages. Categories will include:

- Treatment-emergent adverse event (TEAE);
- Investigational product related (definitely, probably, possibly, unlikely, unrelated);
- Infusion-related allergic reaction;
- Neurological worsening;
- Secondary infection;
- Urinary tract infections;
- Maximum severity of TEAE – mild, moderate, severe, life-threatening, or death; and
- Serious TEAE.

Adverse events will also be summarized by system organ class and preferred term with counts and percentages. Similar summaries will be provided for:

- Serious TEAEs;
- Investigational product-related TEAEs;
- Infusion-related TEAEs;
- Neurological worsening TEAEs; and
- Secondary infections.

Infusion-related TEAEs will be identified on the eCRF. Secondary infections will be identified by a review of the coded adverse events by the medical monitor prior to database unblinding.

Similar adverse event overview and summary tables will be provided for adverse events within 7 days of treatment infusion and within 90 days of treatment infusion.

Analysis listings of SAEs, investigational product-related adverse events, infusion-related allergic reaction adverse events, and neurological worsening adverse events will be provided by treatment group. The analysis listings will include a treatment-emergent flag, reported term, system organ class, preferred term, start date and time, stop date, severity, relation to investigational product, action taken, outcome, seriousness, dechallenge result, and rechallenge result as appropriate.

9.2.2.2 Safety laboratory parameters

Subjects experiencing post-infusion clinically significant laboratory abnormalities will be summarized with counts and percentages. An analysis listing of all randomized subjects with clinically significant safety laboratory parameter abnormalities will be provided by treatment group and will include parameter results and a description of the abnormality.

9.2.2.3 Allogeneic antibody

The presence of a Human Leukocyte Antigen (HLA) antibody will be measured and results will summarized as being positive or negative (number and percentage of subjects) for the antibody reactive against HLA Class I or Class II epitopes. Where indicated, the specificity of antibody reactivity will be reported.

9.2.2.4 Vital signs

Values and changes from Baseline will be summarized for each vital sign parameter at each time point using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum). Baseline is defined as the last pre-infusion assessment.

9.2.2.5 Electrocardiogram parameters

An analysis listing of all randomized subjects with ECG abnormalities will be provided by treatment group and will include a description of the abnormality and values for ECG parameters. Clinically significant abnormalities will be reported as adverse events.

9.2.3 Day 90 Analysis

Once all subjects complete Day 90, the database will be cleaned and locked for the purpose of analyzing the Day 90 efficacy and safety data. An independent, unblinded statistician will perform this analysis and provide the results to a team at Athersys, Inc. No Day 365 endpoints will be included in this analysis and no subject-level data will be provided to Athersys, Inc. or any members of the project team so that the treatment assignment of all subjects remains blinded until completion of Day 365.

After the last subject completes Day 365, the final database will be prepared and the Day 365 analyses will be performed. At this time, members of the study team will become unblinded to subject treatment assignments.

9.2.4 Data Safety Monitoring Board

The DSMB will monitor the safety of subjects over the course of the study. Should any of the protocol stopping rules occur (see Section 4.4), enrollment will be stopped until the DSMB can review the event and determine if it is safe to continue enrollment.

In addition, the DSMB will meet during the subject enrollment period to examine the unblinded safety data. Subjects, Investigators, site staff, and in general all personnel directly involved in the conduct of the study, will remain blinded to the subjects' treatment assignment until the completion of the study.

Details related to the DSMB responsibilities, authorities, and procedures will be documented in the DSMB charter, which will be finalized by the DSMB prior to the first subject being enrolled in the study.

9.2.5 Sample Size Determination

For this study, sample size and power are computed by assuming that the true proportions of subjects with various mRS outcomes at the 90-day follow-up visit are as displayed in Table 1.

Table 1. Estimates of Proportions of Subjects With Modified Rankin Scale Scores – 90-Day Follow-up Visit

	Modified Rankin Scale Score						
Group	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Treatment	4.0%	15.5%	28.9%	26.6%	17.5%	0.0%	7.4%
Control	0.0%	6.8%	27.1%	29.7%	14.4%	5.8%	16.3%

The rates used in the computations correspond to those observed in B01-02 for the population under study in B01-04, making minor adjustments to reflect expectations for subjects receiving both tPA and mechanical thrombectomy (limited to 10% of enrolled B01-04 study subjects). The power of unstratified Wilcoxon rank test was estimated using Monte-Carlo simulation. Based on this approach, a 1-sided alpha level of 0.025, 300 subjects provide 95% power for testing the study's primary effectiveness hypothesis. The power of van Elteren test adjusting for stratification factors will be even higher than this unstratified counterpart.

Other alternative outcome estimates were evaluated (a) adjusting the outcome above by reducing the treatment advantage over control, and (b) comparing an adjusted treatment outcome to placebo rates observed in other relevant studies. Several studies were identified with control populations representative of the targeted population for B01-04, taking into consideration stroke severity, concomitant treatments (e.g., tPA), timing of treatment, age, and functional outcomes.

These sensitivity analyses confirm that at 300 subjects (150 subjects per group), the B01-04 study would be adequately powered to test the hypothesis that MultiStem treatment can improve global disability as measured throughout the range of mRS scores by shift analysis.

Based on previous studies, the proposed study is expected to have a low dropout rate, outside of deaths. Among the subjects randomized in Study B01-02 (n=129), there were 23 who did not complete the study over 365 days. Among these, 3 subjects (2.3%) withdrew consent prior to dosing, 14 subjects died (10.9%), 5 subjects (3.9%) were lost to follow-up, and 1 subject (0.8%) was withdrawn by Investigator. In the proposed study, death is not considered a discontinuation, but rather the worst outcome for the mRS distribution analysis and a non-response for the binary analyses.

In the current study, the discontinuation rate other than death is expected to be approximately 6% to 7%. The power estimation was repeated based on dropout rates of 6% and 10% (a more conservative assumption) using the complete case analysis, assuming that the dropout is completely random. Simulations show the power is marginally reduced after considering the missing data caused by early dropout as presented in the table below. As Table 2 displays, this

analysis suggests that the study is designed to handle anticipated missing data/dropouts in planned analyses of the results.

Table 2. Power Estimations for Various Dropout Rates

Assumed dropout rate	Sample per group	Power				
			Alternative cases for sensitivity analysis			
		Base case	Case 1	Case 2	Case 3	Case 4
0%	150	95%	84%	75%	97%	88%
6%	141	94%	82%	73%	96%	85%
10%	135	93%	81%	71%	95%	84%

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 Code of Federal Regulations Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via manual review, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

11.2.1 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.2.2 Ethics Committee

It is the responsibility of the Sponsor or their designee (i.e., Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject or LAR is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject or LAR before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. Note: Standard of care procedures may be performed prior to written informed consent. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

Determination of whether consent by a LAR is required (and if so, determination of the LAR) as well as specific details of the consenting process will be determined by country law, state law, and local IRB/IEC requirements. The study team is encouraged to use fax and/or telephone and/or telemedicine consent if allowed by country law, state law, and local IRB/IEC rules.

11.4 Subject Card

On enrollment in the study, the subject will receive a subject card to be carried at all times. The subject card will state that the subject is participating in a clinical research study, type of treatment, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki (Seoul 2008) and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE

forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 Code of Federal Regulations Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e., initiation of study centers) when the CTA and favorable ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

12.2 Address List

12.2.1 Sponsor

Athersys, Inc.
3201 Carnegie Avenue
Cleveland, OH 44115
Telephone: 216-431-9900
Fax: 216-361-9495

12.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
Telephone: 513-579-9911
Fax: 513-579-0444

12.2.3 Serious Adverse Event Reporting

Medpace Clinical Safety
Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-0444

12.2.4 Biological Specimens

Medpace Reference Laboratory (US, Belgium, and/or Singapore locations)*
Corporate address:
5365 Medpace Way
Cincinnati, Ohio 45227
Telephone: 513-366-3270
Fax: 513-366-3273
**For specific shipping information refer to the laboratory manual.*

12.2.5 MRI/CT Scans

Imaging Core Lab LLC
5375 Medpace Way
Cincinnati, OH 45227
Telephone: 513-366-3266
Fax: 513-366-3244

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 3. Schedule of Procedures

Study Phase		Baseline (Day 0)		Post-Infusion							
Visit Timing	Screening[1] (0 to 28 hr post-stroke)	Before infusion start	Infusion start (18 to 36 hr post-stroke)	24 hours from infusion start[2] (±6 hr)	48 hours from infusion start[2] (±6 hr)	Day 7[3] (±2 days)/ Day of Discharge	Day 30 (±3 days)	Days 60, 150, 210, 270, and 330 Remote Visits (±7 days)	Day 90 (±7 days)	Day 180 (±7 days)	Day 365 (±7 days)/ Early Termination
Informed consent	X										
Inclusion/exclusion assessment	X	X									
Medical history and demographics	X										
Physical examination[4]	X	X		X			X				X
Weight	X										
Height (measured or reported)	X										
Vital signs	X	X[5]	X[6]	X	X	X					X
Pulse oximetry	X	X[5]	X[6]	X	X	X					X
Hematology and serum chemistry[7]	X	X		X	X	X	X				
Urine or serum pregnancy test	X[8]										
Allogeneic antibody		X					X				
12-lead ECG	X			X	X						
Adverse event assessment/collection			X	X	X	X	X	X	X	X	X
Concomitant medication collection[9]	X	X	X	X	X	X	X	X	X		
NIHSS[10]	X[11]	X[10]				X	X		X	X	X
mRS[12]	X[13]					X	X		X	X	X
Barthel Index[14]	X[15]					X	X		X	X	X
Brain MRI/CT	X										
EQ-5D questionnaire									X		X
Exploratory blood biomarkers		X			X	X					
Spleen ultrasound (sub-study only)		X		X	X	X					
Brain MRI-DTI (sub-study only)	X[16]								X		X
Hospitalization data[17]						X	X	X	X	X	X
Contact CTIRT	X[18]	X[19]									
Infusion			X								
Remote contact								X			
Inquire about rehabilitation activities[20]						X	X	X	X	X	X
Inquire about occupational status[21]											X

1. Screening procedures (including MRI/CT) can potentially be performed as part of standard of care procedures.
2. Visit times are calculated from infusion start time at Day 0.
3. If hospital discharge occurs before the Day 7 window, Day 7 procedures can be performed in the hospital at discharge.
4. The extent of the physical examination is at the Investigator's discretion.
5. Oxygen saturation (via pulse oximetry) and vital signs, including blood pressure, pulse, respiratory rate, and temperature will be collected just prior to infusion start, but no more than 60 minutes prior.
6. Oxygen saturation (via pulse oximetry) and vital signs, including blood pressure, pulse, respiratory rate, and temperature will be collected every 30 (±5) minutes for the first 2 hours after the infusion start and then at 4 hours (±30 minutes) and 6 hours (±30 minutes) after the infusion start.
7. At Screening, hematology and chemistry analyses will be performed per standard of care at each institution (i.e., local laboratories) to determine eligibility. For the remainder of the study, starting at Day 0 (Baseline) all chemistry and hematology blood samples will be collected and sent to a central laboratory.
8. Pregnancy tests will be performed on female subjects of childbearing potential. Urine or serum testing will be performed per standard of care.
9. Concomitant medications will be collected from the time of hospital admission through the Day 90 visit. Note: Concomitant medication use associated with SAEs will be collected through Day 365. Concomitant medications will be recorded at the Early Termination Visit if the visit occurs on or prior to Day 90.
10. NIHSS assessments are preferred to be completed in a face-to-face setting. If conducted remotely, telemedicine is acceptable, and telephone is not acceptable. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance. The Baseline NIHSS score should be determined 18 to 34 hours from the time of stroke onset (final eligibility assessment). Baseline NIHSS assessment should occur ≥6 hours after the last NIHSS assessment at Screening. The Baseline NIHSS score should not have changed by ≥4 points from the Screening NIHSS. The Baseline NIHSS score should be confirmed prior to randomization. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible.
11. The Screening NIHSS score used for determination of eligibility should be collected as soon as possible following admission to the hospital. In the event a subject receives concomitant reperfusion therapy the subject's Screening NIHSS score is encouraged to be collected prior to any concomitant reperfusion therapy but can be collected as late as 4 hours following completion of the last reperfusion (mechanical or pharmacologic) therapy.
12. The mRS assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual subject when possible. When evaluating subjects to determine the mRS score, the raters of the score must not make any attempt to exclude or correct for disability that the rater attributes to causes other than stroke. The score should be recorded without regard to the cause of the disabilities that impact the score or time point at which the disabilities occurred.
13. The mRS score determined at Screening is based on historical values prior to the onset of symptoms of the current stroke by either self-reported history or family/caregiver report while scores at subsequent visits are based on values obtained following the onset of the current stroke.
14. Barthel Index assessments are strongly preferred to be completed in a face-to-face setting. If face-to-face assessment is not possible, assessments may be conducted remotely by telemedicine. Only as a last resort in extraordinary circumstances, if telemedicine is not possible, telephone assessment is permitted. The possibility of a remote visit and the procedures to be conducted need to be discussed with the Sponsor in advance. Effort should be made to have the same assessor complete all post-Baseline visit assessments for an individual when possible.
15. The Screening Barthel Index score is based on historical values prior to the onset of symptoms of the current stroke by either self-reported history or family/caregiver report. The Screening Barthel Index score can be collected any time prior to the start of the infusion.
16. The Baseline brain MRI-DTI can be completed at any time prior to the start of the infusion.
17. Collect the dates of admission to and discharge from the intensive care unit, hospital, and non-hospital residential care facility from the time of initial stroke hospital admission through Day 365.
18. If the subject is a screen failure, a blinded team member should contact Medpace CTIRT to register the subject as a pre-randomization failure.
19. The blinded team member should randomize patient then an unblinded team member should contact Medpace CTIRT to acquire the treatment group assignment.
20. Subject will be asked about any healthcare and rehabilitation activities that have taken place (e.g., inpatient physical therapy, outpatient physical therapy, etc.).
21. Subject will be asked about occupational status (e.g., inpatient physical therapy, outpatient physical therapy).

CT = computed tomography; CTIRT = ClinTrak® Interactive Response Technology; DTI = diffusion tensor imaging; ECG = electrocardiogram; EQ-5D = EuroQol 5 dimensions; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

APPENDIX B: DEFINITIONS AND MANAGEMENT OF INFUSION RELATED ALLERGIC REACTIONS

In the event of allergic/hypersensitivity reactions, Investigators should institute treatment measures according to best medical practice.

Any event of infusion-related reaction or allergic response, generally defined as clinically significant deviations in blood pressure, pulse, respiratory rate, and oxygen saturation, will be recorded.

In the event of infusion-related allergic reaction and if flushing, sudden rash, or difficulty breathing occur, the infusion will be stopped immediately, and affected subjects will be monitored until the infusion-related allergic reaction has resolved.

The following treatment guidelines may be employed at the discretion of the treating physician:

Grade 1 infusion-related reaction (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.0): Mild transient reaction; infusion interruption not indicated; intervention not indicated.

Grade 2 infusion-related reaction (NCI-CTCAE v4.0): Therapy or infusion interruption indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤24 hours.

1. Decrease infusion rate by 50%, administer antihistamines, corticosteroids, etc. as medically indicated and monitor for worsening condition;
2. Stop infusion if infusion-related symptoms continue despite #1;
3. Administer bronchodilators, oxygen, antihistamines, corticosteroids etc., as medically indicated;
4. Resume infusion at 50% of previous rate once reaction has decreased to Grade 1 in severity. Monitor closely for any worsening; and
5. If the reaction reoccurs, stop infusion. Study treatment will be discontinued.

Grade 3 infusion-related reaction (NCI-CTCAE v4.0): Characterized as prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.

Grade 4 infusion-related reaction (NCI-CTCAE v4.0): Characterized as life-threatening consequences; urgent intervention indicated.

Treatment of Grade 3 or Grade 4 infusion-related reactions:

1. Stop the infusion immediately and disconnect infusion tubing from the subject;
2. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, IV fluids, vasopressor agents, oxygen, etc. as medically indicated;
3. Immediately contact Medpace Medical Monitor and report serious adverse event to Medpace; and
4. Study treatment will be discontinued.