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SYNOPSIS

Title	Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study of Efficacy and Safety of Trans Sodium Crocetinate (TSC) Administered Onboard Emergency Vehicles for Treatment of Suspected Stroke: PHAST-TSC
Protocol No.	100-501
Study Phase	2
Study Design	Double-blind, randomized, placebo-controlled, phase 2 preliminary efficacy and safety trial of Trans Sodium Crocetinate (TSC) as first-line treatment of suspected stroke subjects in the emergency vehicle.
Study Population	Ambulance-transported subjects identified as having an acute stroke using the modified Los Angeles Prehospital Stroke Screen (mLAPSS) screen, who are within 2 h of last known well time.
Number of Subjects	160 subjects that meet all protocol inclusion/exclusion criteria.
Study Centers	Up to 30 stroke receiving hospitals.
Objective	To assess the potential efficacy and safety of TSC as early treatment for both ischemic and hemorrhagic stroke when administered while subject is in ambulance being transported to hospital.
Endpoints	Primary Efficacy Endpoint: • Global disability level on the utility-weighted modified Rankin Score (UW-mRS) Assessment at 90 days in all subjects Secondary Efficacy Endpoints: • Functional independence (mRS 0-2) in all subjects • Global disability level on the UW-mRS in ischemic stroke subjects • Functional independence (mRS 0-2) in ischemic stroke subjects Exploratory Efficacy Endpoints: • Freedom from disability (mRS 0-1) • Barthel Index (BI) • National Institutes of Health Stroke Scale (NIHSS) • Stroke Impact Scale (SIS-16) • AMC-Linear Disability Scale

2 STUDY METHODS

2.1 Rationale

Neuroprotection is a promising treatment strategy, complementary to reperfusion. Neuroprotective agents interrupt the cellular, biochemical and metabolic processes that mediate cerebral tissue injury during or following exposure to ischemia. Since they are safe and potentially beneficial in hemorrhagic as well as ischemic stroke, neuroprotective agents can, in principle, be given prior to brain imaging, including in the prehospital setting, to stabilize threatened tissues until definitive rescue by therapeutic or spontaneous reperfusion. In past studies, more than 70 neuroprotective agents were tested in randomized controlled clinical trials in acute ischemic stroke and none were found unequivocally beneficial in definitive Phase 3 trials (Kidwell et al, 2001; Moretti et al, 2015). However, the crucial factor of delayed time to treatment hindered almost all trials. Although it is in the first 2 h that neuroprotective agents are most beneficial in rodent and primate focal stroke models, no prior pivotal human clinical neuroprotective agent trial before the FAST-MAG trial enrolled any substantial cohort of subjects in this time window (Ferguson et al, 2004). The FAST-MAG trial (Saver et al 2014; Saver et al, 2015), which utilized magnesium sulfate as the tested neuroprotective agent, did enroll 1700 subjects in a Phase 3 trial. Although the tested agent had neutral effects, the trial demonstrated that ambulance start of neuroprotective study agents in suspected stroke subjects allows rapid attainment of serum target levels, in the time period when the greatest volume of threatened tissues is still salvageable (Shkirkova et al, 2017). Building upon this successful protocol for field agent delivery, the current trial will test a new neuroprotective agent. TSC, a different type of neuroprotective agent, has shown positive results in animal models of stroke.

The ideal neuroprotective agent for stroke would have few adverse side effects and be safe and potentially beneficial in both ischemic and hemorrhagic stroke. Diffusion Pharmaceuticals Inc. has developed TSC, indicated as a drug to treat hypoxia by selectively enhancing the re-oxygenation of hypoxic tissues. The ability of TSC to increase the diffusion (movement) of oxygen is the underlying mechanism by which TSC exerts its pharmacodynamic effects. In vitro studies demonstrate that TSC increases the diffusion of oxygen by altering the molecular arrangement of the water molecules which constitute the bulk of blood plasma. This effect creates a more ordered water structure which is less dense, reducing resistance to oxygen diffusion and allowing a more rapid movement of oxygen through the plasma (Laidig et al., 1998; Stennett et al., 2006). This is the reason for the ability of TSC to increase the diffusion of oxygen through blood plasma to hypoxic tissues.

Since FAST-MAG established that an ambulance-based study could be done successfully and enable agent delivery in the early time window when benefit was maximal in preclinical models, it is deemed appropriate and advantageous to do a similar study using

TSC as the neuroprotective agent. TSC can be easily administered and has been shown to be safe thus far in both animal and human trials.

2.2 Design Overview

This is a multicenter, randomized, placebo-controlled, double-blind, parallel group trial of intravenous trans sodium crocetinate (TSC) initiated by paramedics in the field within 2 hours of symptom onset in 160 subjects with acute stroke. The primary objectives of the study are to evaluate the efficacy and safety of field-initiated TSC in improving the long-term functional outcome of subjects with acute stroke. Subjects with acute stroke will be identified in the field by emergency medical service responders who have received training in basic and advanced cardiac life support, stroke recognition, and specific procedures relevant to the proposed study. Paramedics will deliver the single, field, bolus dose of study agent, TSC at 0.25 mg/kg or matched placebo, followed after hospital arrival by standard of care (SOC). No additional study drug will be administered in the hospital. Follow-up assessments will be performed at Emergency Department (ED) arrival, 24 hours, 48 hours, Day 4, Day 30, and Day 90. The study will be performed at up to 30 receiving hospital sites.

Across all preclinical models and in human acute ischemic stroke, the relation between time from onset and response to beneficial therapy in acute ischemic stroke is a graded one of continuous decline with time, rather than square-shaped, characterized by uniform high benefit until a sudden drop to no benefit at a particular time point. Across all neuroprotective and reperfusion treatments in preclinical models, and for both the proven human reperfusion therapies (IV fibrinolysis and endovascular mechanical thrombectomy), treatment is most efficacious if started at 30 mins rather than 60 mins, at 1h rather than 2h, at 2h rather than 3h, and at 3h rather than 4h.

A consequence of this graded relationship is that the sample sizes required to detect beneficial effect of a treatment agent are moderate for subjects treated sooner after onset, when the magnitude of benefit is largest. But the sample sizes required to detect beneficial effect of a treatment agent are extremely large for subjects treated near the end of the therapeutic window, when the magnitude of benefit is small.

As a result, successful development programs for treatments for acute ischemic stroke have used a “sweet spot and expand” strategy. For tPA (atleplase, Activase), initial US trials stratified therapy in the 0-90m and 91-180m window. Later trials explored the 181-270m and 271-306m window. Similarly, for endovascular mechanical thrombectomy, the initial US registration trial evaluated the 0-6h window only for clinical benefit, even though the devices were cleared for technical use up to 8h after onset. Conversely, many of the unsuccessful trials of neuroprotective agents in the past did not follow this approach, and enrolled subjects

up to 4h or more after onset, likely resulting in their being severely underpowered to detect the smaller treatment effects potentially present in late enrolled subjects.

Based on the above considerations, the current trial was designed to enroll subjects within 2h of onset, when the magnitude of benefit from TSC is likely to be larger and more feasibly detectable. The trial was designed to be performed in the prehospital setting, because that is the only setting in which treatment within the 2h time window in large numbers of subjects has been shown to be attainable. We anticipate that, should the initial under 2h treatment study indicate robust therapeutic benefits persisting up to the 2h administration timepoint, we will in the future perform additional trials with later, 2-4h, enrollment windows, and that those could be performed in the Emergency Department setting.

Diffusion investigated many approaches to blinding this trial and it was determined that it would be very difficult because of the highly colored nature of the test article and the necessity for it to be delivered by emergency medical personnel in an ambulance setting. Amber syringes are designed to deliver much larger volumes or ones which are for other purposes, such as oral dosing of liquids to animals. The dosages in this stroke study vary from less than 1 mL to over 2 mL, depending on body size. That can be accommodated with a standard 3 mL syringe. A manufacturer who, upon Diffusion's request, attempted to make 3 mL amber syringes gave up after a month because they found that they could not put volume markings on the syringes, rendering them useless for this trial. Moreover, even if amber syringes were available, the emergency medical personnel would almost certainly be able to observe the coloration of the test article while administering the injection. Thus, the TSC injections will be prepared and injected by unblinded personnel on each ambulance. All other study personnel will be blinded (see Section 2.9).

2.3 Study Objectives

2.3.1 Primary Efficacy Objective

The primary efficacy objective is to test the hypothesis that treatment with TSC reduces the level of long-term disability of hyperacute stroke subjects. The study endpoint analysis to evaluate this hypothesis will be the difference in distribution of scores between TSC and placebo groups on the utility-weighted modified Rankin Scale (UW-mRS) measure of global disability, assessed 90-days post-stroke.

2.3.2 Secondary and Exploratory Efficacy Objectives

A secondary efficacy objectiveis to test the hypothesis that treatment with TSC improves the long-term outcome of hyperacute stroke subjects in achieving functional independence (mRS 0-2) at 90 days.

Additional secondary efficacy objectives are to test the hypothesis that treatment with TSC improves the long-term outcome of patients with final diagnosis of acute cerebral

ischemia in reducing the level of long-term disability (assessed with the UW-mRS endpoint) and in achieving functional independence (assessed with the mRS 0-2 endpoint).

Exploratory efficacy objectives are to evaluate for signals of benefit of treatment with TSC upon freedom from disability (mRS 0-1) at 90 days, activities of daily living (Barthel Index [BI]) at 90 days, neurologic deficit (National Institutes of Health Stroke Score [NIHSS]) at 90 days, and quality of life (Stroke Impact Scale [SIS-16] and AMC-Linear Disability Scale) at 90 days.

2.3.3 Primary Safety Objective

The primary safety objective is to test the hypothesis that treatment with TSC is not associated with increased occurrence of serious adverse events in hyperacute stroke subjects. The study endpoint analysis to evaluate this hypothesis will be comparison of the frequency of SAEs in the TSC and placebo groups.

2.3.4 Secondary and Exploratory Safety Objectives

Secondary safety objectives are to test the hypothesis that treatment with TSC is not associated with increases in any organ-specific classes of serious adverse events or increased mortality.

2.4 Study Population

All suspected stroke subjects transported by Emergency Medical Services (EMS) in the participating catchment areas will be screened for study entry. Subjects in the study will be subjects with newly diagnosed stroke as determined by modified Los Angeles Prehospital Stroke Screen (mLAPSS) who are ready for transportation to hospital.

2.4.1 Inclusion Criteria

1. Age 40-85, inclusive
2. Last known well time 15-120 minutes before anticipated study drug injection
3. Suspected stroke identified by the Modified Los Angeles Prehospital Stroke Scale (mLAPSS)
4. Moderate to severe motor deficit, with Los Angeles Motor Scale (LAMS) 2 or higher
5. No seizure

2.4.2 Exclusion Criteria

Subjects are not eligible if they meet any of the following criteria:

1. Coma
2. Rapidly improving neurologic deficit
3. History of seizures or epilepsy

4. Pre-existing neurologic, psychiatric, or advanced systemic disease that would confound the neurological or functional outcome evaluations
5. SBP < 90 or > 220
6. Major head trauma in the last 24 hours
7. Recent stroke within 30 days
8. Known to be pregnant or lactating

2.5 Pregnancy Screening

Because of the difficulty of performing a pregnancy screening, a Follicle Stimulating Hormone (FSH) test or gathering information regarding menstruation history in an ambulance environment, emergency medical personnel who are engaged in early assessment of a potential female stroke subject will ask the subject, or if the subject is unable to respond, those who may be associated with her, whether she is, in fact, pregnant. Subjects for whom the answer is affirmative will be excluded from enrollment in the trial. Female subjects younger than 55 and considered of child bearing potential will receive a screening for pregnancy at the hospital as part of standard of care.

Women are considered past the age of "child-bearing potential" if they are greater than 55 years of age, OR if they are at least 50 years of age AND have not menstruated for at least 12 months, and have a documented FSH level of greater than 40 mIU/mL, OR they are at least 45 years of age AND have not menstruated for at least 18 months, OR have a documented FSH level of greater than 40 mIU/mL.

Details of pregnancies in female participants and female partners of male participants will be collected after study drug treatment and until study completion (Day 90 visit or early termination). If a pregnancy is reported or discovered, the investigator should inform the Sponsor or designee within 24 hours of learning of the pregnancy. Pregnancy itself is not considered an AE or SAE, however abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported to the sponsor. If a pregnancy is reported, the Sponsor or designee will follow up on pregnancy outcome 4 weeks after the projected due date.

2.6 Enrollment and Consent

Subjects are initially enrolled in this study in the ambulance with hours of enrollment between 06:00 to 22:00. Effort will be made to obtain prospective informed consent when deemed to be feasible. If not feasible, subjects will be enrolled under regulations for exception from explicit informed consent (EFIC) in emergency research circumstances, after public disclosure and community consultation. Written informed consent to continue in the study is obtained from subjects or their legally authorized representatives as soon as possible after hospital arrival. Acute stroke is an extremely time-urgent medical emergency. The two standard of care therapies for acute ischemic

stroke, intravenous tissue plasminogen activator (tPA) and endovascular mechanical thrombectomy, both are extremely time-sensitive.

Diffusion has consulted extensively with our clinical investigator team. Based on these extensive discussions we have elected to incorporate the requirement for a thoroughly documented affirmative agreement process prior to study participation for all subjects to the extent that they can communicate, and/or their legally authorized representative, if they are on-scene. We believe this process will allow for an effective balance between timely treatment delivery and patient informed consent.

Several developments have transpired in the years since the FAST-MAG trial completed enrollment in December 2012 that make obtaining prospective informed consent in the field within the therapeutic window, as performed in FAST-MAG, no longer ethical to pursue.

1. Interval studies have demonstrated an extreme time-dependency for the benefit of intravenous tissue plasminogen activator. Every 9-minute delay in IV tPA treatment start results in 1 out of 100 treated subjects having a worse outcome (Saver et al, 2013; Kim et al, 2017). These studies established unequivocally that IV tPA treatment benefit declines very rapidly. As a result, even just the several minutes required for a rapid explicit written informed consent process would jeopardize subject safety by delaying start of IV tPA.

2. Interval studies have demonstrated that endovascular thrombectomy is an extremely beneficial therapy for acute ischemic stroke (Goyal et al, 2016). In addition, studies have demonstrated that the time-dependency for the benefit of endovascular thrombectomy is even more extreme than that for IV tPA. For endovascular mechanical thrombectomy, every 4-minute delay in treatment start results in 1 out of 100 subjects having a worse outcome (Saver et al, 2016). As a result, even just the several minutes required for a rapid explicit written informed consent process would jeopardize subject safety by delaying start of endovascular mechanical thrombectomy.

3. The two multicenter clinical trials of prehospital treatment for acute stroke launched in the last 5 years have used solely EFIC enrolling, without explicit informed consent: the RIGHT 2 trial of glyceryl trinitrate in Great Britain (ISRCTN26986053) and the FRONTIER trial of NA-1 in Canada (NCT02315443). These trials demonstrate that an international consensus recognizes it is no longer feasible to pursue explicit informed consent, rather than EFIC, in prehospital neuroprotective stroke trials, because delay of standard therapies jeopardizes subject safety.

As directed by FDA regulations regarding EFIC research, representatives of the communities in which the research will be conducted and from which the subjects will be

drawn will be consulted before research begins, and all plans for the research, its risks, and expected benefits will be publicly disclosed. These requirements will be performed by establishing community advisory committees, extensive public education conferences, newspaper advertisements, and mailings.

If a written informed consent process does not take place prior to drug injection, a brief thoroughly documented verbal or non-verbal affirmative agreement for study participation will be elicited from subjects (to the extent that they can communicate) and/or from their legally authorized representatives (LARs – e.g. close family member, legal guardian) if they are on scene. Paramedic training will be focused on all enrollment processes in which they will participate. The training will include didactic coverage of the regulatory framework of EFIC trials, the distinction between affirmative agreement and consent, how to behaviorally assess for affirmative agreement, and the importance of communicating key aspects of their affirmative agreement evaluation when they give the phone report to the PHAST-TSC central enrolling physician who will be making the final decision regarding enrollment in the trial, and authorizing opening of study kit. In addition, all of the central enrolling physicians in the study will also be trained regarding these aspects. If not obtained in the ambulance, once the subject arrives at the hospital a full written informed consent process will be performed by a competent consent-provider.

Among enrolled subjects, the following procedures will be utilized to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation, and other information contained in the informed consent document. A physician-investigator or study coordinator will interview and examine the subject upon arrival in the Emergency Department. During this encounter, the physician-investigator and study coordinator will both assess subject competency and work with hospital staff and social services to identify and contact a legally authorized representative and family members. The physician-investigator and study coordinator will continue these efforts throughout the duration of the study. As soon as a subject regains competency, or a legally authorized representative or a family member has been contacted, the physician-investigator will inform him or her of the subject's inclusion in the clinical investigation, the details of the investigation, and other information contained in the informed consent document; and that the subject's participation in the study may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled.

A physician-investigator or study coordinator will examine the subject at ED arrival, 24 hrs, 48 hrs, 4 days, 30 days, and 90 days after hospital arrival. If the exam demonstrates that the subject's condition has improved and the subject has regained competency the physician-investigator will inform the subject of his or her inclusion in the clinical investigation, the details of the investigation, and other information contained in the

informed consent document; and that the subject's participation in the study may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the subject is entered into the study and dies before the subject's legally authorized representative or family member can be contacted, the physician-investigator and study coordinator will continue efforts to identify the subject's legally authorized representative or a family member, working with hospital administration, the coroner's office, and other appropriate personnel. Once the legally authorized representative or family member is identified and contacted, the physician-investigator will discuss with them the essential elements of the clinical investigation.

As required by FDA regulations, the investigators will summarize efforts made to contact legally authorized representatives in each case and make this information available to the local Investigational Review Board (IRB) at the time of continuing review.

2.7 Randomization

This protocol is using the step-forward, pre-encounter method of randomization that has been developed for rapid availability of research study agents in emergency trials. Each ambulance will be carrying only one study kit at any time, the next kit in its permuted random block sequence. Randomization will be 1:1 between active TSC and placebo. When that ambulance enrolls a subject, the subject will be assigned to the treatment group of the study agent kit the ambulance is carrying at the time. Subjects will be considered enrolled in the trial upon study drug injection.

A Schedule of Events is included as an Appendix 8.1 to this protocol.

The study design is shown in Table 4.

Table 4. Study Design

On Ambulance
Within 2 hours of first stroke symptoms

- Perform mLAPSS
- Determine study eligibility in consultation with PHAST-TSC central enrolling physician
- Explicit informed consent or EFIC enrollment
- Perform GCS; Los Angeles Motor Scale (LAMS); Paramedic Global Impression of Change Score (PGIC)
- Obtain heart rate; blood pressure; body weight estimate
- Administer study drug (TSC or placebo) as IV injection

Emergency Department Arrival

- Informed Consent, if enrolled by EFIC
- SOC demographics; heart rate; blood pressure; body weight; pregnancy screening; labs (hematology, chemistry, coagulation); troponin
- SOC brain imaging done within 48 hours of Emergency Department arrival
- Performs mRS; BI; NIHSS
- tPA dose
- Concomitant medications/therapies
- Adverse events

24 Hours

- Obtain Informed Consent if enrolled by EFIC and not obtained at previous visit
- SOC heart rate; blood pressure; labs (hematology, chemistry, coagulation); troponin
- SOC body weight; pregnancy screening if not obtained during previous visit
- Concomitant medications/therapies
- Adverse events
- Performs NIHSS

48 Hours

- Obtain Informed Consent if enrolled by EFIC and not obtained at previous visit
- SOC heart rate; blood pressure; labs (hematology, chemistry, coagulation); troponin
- Concomitant medications/therapies
- Adverse events
- Performs NIHSS

Day 4 (If discharged prior, by phone)

- Obtain Informed Consent if enrolled by EFIC and not obtained at previous visit
- SOC heart rate; blood pressure; labs (hematology, chemistry, coagulation); troponin
- Concomitant medications/therapies
- Adverse events
- Performs mRS; BI; NIHSS

Day of Discharge

- Concomitant medications/therapies
- Adverse events
- Discharge date and destination

Day 30 (± 6 days) Follow-up (by phone)
To be performed by a Study Coordinator blinded to subject and subject chart:
- Obtain Informed Consent if enrolled by EFIC and not obtained at previous visit
- Concomitant medications/therapies
- Adverse events
- mRS; BI

Day 90 (± 14 days) Follow-up
To be performed by a Study Coordinator blinded to subject and subject chart:
- Obtain Informed Consent if enrolled by EFIC and not obtained at previous visit
- Concomitant medications/therapies
- Adverse events
- mRS; BI; NIHSS; LAMS; Stroke Impact Scale (SIS-16) Quality of Life Assessment and AMC-Linear Disability Scale (AMC-LDS)

2.8 Withdrawal of Subjects

2.8.1 Criteria for Early Withdrawal

The following events are considered sufficient reason to discontinue a subject from the study:

- Subjects are free to withdraw from the study at any time, for any reason, and without prejudice.
- The subject is non-compliant.
- The subject experienced an AE that in the investigator's opinion precludes continued participation.
- The subject incurred a significant protocol violation that constitutes a safety hazard or significantly confounds the interpretation of the data from that subject.
- At the Sponsor's request.
- The study is terminated.

2.8.2 Subjects Lost to Follow-up

The investigator will attempt to contact any subject that fails to return in order to evaluate the reason the subject has not returned and to obtain follow-up safety information. All attempts to contact the subject should be documented, including the use of registered mail with return receipt.

2.8.3 Replacement of Subjects

Subjects who have received TSC or placebo will not be replaced.

2.14.9 CT/MRI

Image scans of all CTs/MRIs obtained within 48 hours of ED arrival will be obtained for independent neuroradiologist review.

3 ADVERSE EVENT REPORTING

3.1 Definitions

3.1.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related. An AE is any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. This includes changes in anatomical, physiological, or metabolic functions as indicated by physical examination signs, symptoms, and/or laboratory changes or medical occurrence which develops or worsens while enrolled in this study regardless of whether the event is considered related to the investigational drug. Enrolled is defined as a subject that is assigned to treatment and is dosed with TSC or placebo.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. The Sponsor or designee will evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the AE.

Events occurring before the first TSC dose are to be considered pre-existing conditions and should be recorded as medical history. Unless a worsening occurs, they should not be considered AEs.

Abnormal laboratory values or test results constitute AEs only if they are considered clinically significant and are associated with clinical signs or symptoms or require therapy. Clinically significant abnormal laboratory values will be documented in the subject's case report form (CRF). Neurologic worsening, defined as a ≥ 4 point worsening on the NIH Stroke Scale, will be captured as an AE or SAE per the medical opinion of the investigator.

Events **not** considered to be AEs are:

- Hospitalization for treatment which was elective or pre-planned for a pre-existing condition that did not worsen

Events **not** considered to be SAEs are:

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of serious and not resulting in hospital admission.

- Hospital admissions less than 24 hours in duration.

3.1.2 Serious Adverse Events

Serious adverse events (SAEs) are AEs that pose a threat to the subject's life or functioning based on the following outcome/actions regardless of whether the event is considered related to the investigational drug:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other events, based on medical judgment, which jeopardize the subject and require medical/surgical intervention to prevent one of the outcomes above.

3.1.3 Unexpected

Any adverse event where the nature, specificity or frequency of the event is not consistent with either: 1) the known or foreseeable risk associated with the procedures involved in the research that are described in the protocol or Investigator Brochure; or 2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Refer to Appendices, Section 8.3 for the PHAST-TSC List of Expected Adverse Events.

3.1.6 Adverse Event Reporting Requirements

Each subject will be evaluated for the development of AEs. It is the responsibility of the investigator to document all AEs occurring during this investigation, whether or not the AE is considered drug-related. All AEs will be reported to the Sponsor via the CRF. Non-serious AEs will be reported from study drug administration through hospital discharge. SAEs will be reported from study drug administration through study completion (Day 90 visit or early termination). SAEs require expedited review and will be reported by the site to the Sponsor or designee by telephone or electronically within 24 hours of discovery. The nature of each event, date and time of onset, outcome, frequency, intensity, action taken with respect to dosage, whether it was serious or non-serious, and relationship to treatment should be documented. Signs and symptoms should be grouped into a single diagnosis and reported as a single AE when appropriate. SAEs should be followed by the investigator to resolution, or, if the SAE is not expected to resolve, it should be followed until stabilization.

AEs should be documented in terms of a medical diagnosis(es) when possible. AEs not previously documented at Baseline as pre-existing conditions will be recorded in the CRF.

The following definitions will be utilized when classifying AEs:

3.1.6.1 Severity

- Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

3.1.6.2 Relatedness

- Unlikely or Not Related: The adverse event is doubtfully related or clearly not related to the investigational agent/procedure – i.e. another cause of the event is most plausible; and\or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.
- Possibly Related: The adverse event may be related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- Probably Related: The adverse event is likely related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and is unlikely to be attributed to the known characteristics of the subject's clinical state.
- Definitely related: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and that could not be reasonably explained by the known characteristics of the subject's clinical state.