PART A - THE STUDY

PROTOCOL TITLE: The title on the protocol front sheet should specify the study design, aim, the disease to be studied, all test articles to be used in the study, devices as well as medications, dosages (regimens and frequency), the administration route, and subject type (the study acronym may also be included). See example in Appendix A.

PROTOCOL APPROVAL: The protocol approval page should follow the title page. This page should note approval signatures with dates from: Sponsor representatives as appropriate, the Principal Investigator and Co-Investigator(s), Biostatistician, and other appropriate parties. See example in Appendix B.

PROTOCOL SYNOPSIS AND SCHEDULE OF ACTIVITIES (Appendix D): Provide a table that describes the protocol number, protocol title, acronym of study/title if different, clinical phase, investigators study centers, study period, study objective, study population, study design, numbers of subjects, eligibility criteria, route/dosage form, dosage, duration of treatment, primary outcome measures, secondary outcome measures, and sample size consideration.

Provide a table that summarizes the study design, the timing of visits, examinations, laboratory tests, other sample collection(s), adverse event monitoring, and other procedures.

INVESTIGATOR AGREEMENT: This page should follow the protocol approval page. Sample text is provided in Appendix C.

1. INTRODUCTION

1.1. Background

In order to understand the rationale for the study, provide sufficient background information on the development of the drug, its potential role in the disease process being studied, and relationship to current medical treatment.

1.2. Clinical Experience

Present the relevant background information regarding pharmacological and toxicological properties of the compound, previous efficacy and safety experience, and information on alternative therapies.

Based on previous clinical experience, describe the rationale for doing the study in this particular population.

The above information should be study specific and not a reiteration of the Investigator's Brochure. Where relevant, reference publications and the Investigator's Brochure.

2. STUDY OBJECTIVE

2.1. Primary Objective

State clearly and unambiguously the primary objective(s) of the study, indicating what variables will be utilized to satisfy the objective. All objectives should be scientifically sound and achievable. Exploratory studies undertaken early in the development of the compound may have many objectives (Phase 1), whereas in confirmatory studies (Phases 2-4), they may be limited.

2.2. Secondary Objective (only include if applicable to study)

2.3. Additional Objectives

Described any additional objectives, i.e., related to safety and tolerability, or exploratory objectives.

3. STUDY DESIGN

3.1. Overview

This is a **brief** overview of the study design and is intended to indicate how the objective(s) will be achieved.

Comment on the type of study, i.e., single center or multicenter, double-blind (DB), randomized, crossover or parallel group, the type of control (placebo, active), specific treatment groups, method of subject assignment, and the sequence and duration of the study periods.

Display the design diagrammatically and refer to it, when necessary, in the narrative (see APPENDIX D - Schedule of Activities).

3.2. Discussion of Study Design

3.2.1. Rationale for Study

Provide reasons why this study design was chosen, explain how critical decisions on study design were derived and describe any atypical features of the design. Include known or potential problems with the design. Include discussion of the hypothesis and study objectives and why specific primary/secondary variables were chosen.

3.2.2. Rationale for Dosage

Describe the study drug route of administration and dosage with supporting evidence for why it was chosen, (e.g., [DRUG NAME] is being given IV over 30 minutes based on volunteer studies in elderly subjects in which it was well tolerated). Address the necessity for specified lengths of run-in, treatment, and post-treatment follow-up periods, if appropriate.

Describe methods to minimize bias on the part of subjects, investigators, and analysts.

4. STUDY POPULATION

4.1. Subject Numbers (Shaded: Recommended Wording)

State the approximate number of subjects required to complete the study, the approximate number of sites planned, and the approximate number of subjects who will be randomized to receive study drug.

Define the population from which these subject samples will be selected.

See Section 12 for justification of the selected sample sizes.

4.2. Inclusion Criteria

Individually list the criteria that each subject must satisfy to enter the study. The Inclusion Criteria should define the eligible subject population in terms of age, sex, race (as appropriate), diagnosis requirements, method of diagnosis, treatment requirements, degree of symptomatology, ability to perform study-related functions, and the ability to give informed consent.

The criteria should be sufficiently detailed to ensure that the type of subjects entered is appropriate for the study.

4.3. Exclusion Criteria

Individually list the criteria that will prevent inclusion of the wrong subject into the trial. These should not simply be the opposite of the inclusion criteria. Consider previous and current disease, existing or previous therapy, disease severity, pregnancy, fertility, participation in other investigational drug studies, and a time frame for entry after discontinuing disallowed medications.

The criteria may be listed in separate sections according to which stage they apply, e.g., entry to baseline, entry to treatment.

Note: Inclusion and Exclusion Criteria should be stated clearly and unambiguously. Where possible, refer to factual data, not opinions, which can be recorded in Case Report Forms (CRFs).

4.4. Discussion of Subject Characteristics

Present a brief discussion of why the inclusion/exclusion criteria were selected and why non-obvious criteria were selected. This should indicate that the criteria are designed for a specific disease entity and population and does not put the subject's safety at risk.

4.5. Warnings/Precautions (only include if applicable to study)

State and specify warnings, precautions, or contraindications that the subject and Investigator need to be aware of, e.g., diet restrictions, exercise, etc.

Check that the above warnings/precautions are consistent with the Investigator's Brochure.

5. STUDY PROCEDURES

This section will describe, in detail, how the study should be conducted.

Define, if applicable, the particular criteria that must be satisfied before a subject moves from one phase of the study to another and indicate any decision points.

Describe each scheduled visit individually.

5.1. Schedule of Activities
(Shaded: Recommended Wording)

See Appendix D for Schedule of Activities.

5.2. Subject Identification Numbers

5.2.1. Subject Identification (ID) Number
(Shaded: Recommended Wording)

A Subject ID Number will be assigned in sequential order by the site from a list provided to the site by the CTCC. This 4-digit number will be used to identify the subject on all study forms and lab specimens.

5.2.2. Enrollment Identification (ID) Number
(Shaded: Recommended Wording)

An Enrollment ID Number will be assigned at the randomization visit to confirm enrollment and proper receipt of the randomized study drug assignment. The Enrollment ID Number will be the same as the randomization/drug kit number on the study drug container.

5.2.3. CTCC UNIQUE IDENTIFICATION (ID) NUMBER
(Shaded: Recommended Wording)

Subjects will be instructed how to obtain a 9-digit Unique Identification Number at the Screening Visit. This ID system has the ability to track individual subjects across multiple CTCC studies without storing any personally identifiable information. The protected system uses an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, and mother's maiden name), and produces an electronic "fingerprint" output. The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The subject is then assigned a 9-digit CTCC Unique ID Number that is associated with their electronic "fingerprint."

Once a subject signs the informed consent he/she will be directed to a secure website where he/she or the site Study Coordinator (if the subject requests/prefers) will enter the subject's nine data elements. The CTCC Unique ID Number will be printed and provided to the subject.

The Study Coordinator will record this number on the CTCC Unique ID CRF.

In studies where there is a high degree of sensitivity associated with the confidentiality of subject identification, (e.g., at risk HD) it will not be considered a protocol deviation if the subject refuses the creation of the CTCC Unique ID. In this case, the corresponding field on the CRF will be left blank. A note to file should be placed in the subject's source documentation.

If a subject has participated in previous CTCC studies and already has an existing CTCC Unique ID Number, this number will be used for this study. A subject can regenerate his/her CTCC Unique ID Number. He/She can return to the secure website, enter the same nine data elements in the exact same way they were entered the first time and will receive their same CTCC Unique ID Number.

5.3. Screening Visit (Visit SC)

List and describe activities to be conducted

5.4. Baseline Visit (Visit BL)

List and describe activities to be conducted.

5.5. Visit 01

List and describe activities to be conducted.

5.6. e.g., Visit 02

List and describe activities to be conducted.

5.7. e.g., Telephone 01 (if applicable)

List and describe activities to be conducted.

5.8. e.g., Visit n, etc.

List and describe activities to be conducted.

5.9. Final Visit (Visit XX)

Define specifically the final visit for the study (i.e., final in-person visit and/or telephone contact) and define which visit/contact denotes study conclusion.

List and describe activities to be conducted.

5.10. e.g., Unscheduled Visits

Discuss the circumstances for an unscheduled visit and what procedures and evaluations should occur.

(Shaded: Recommended Wording)

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the site Investigator. The date and reason for the unscheduled visit will be recorded in the source documentation.

5.11. e.g., Premature Withdrawal (Visit PW) (Subject Withdrawal or Permanent Discontinuation of Study Drug) (Shaded: Recommended Wording)

Subjects have the right to withdraw from the study at any time without prejudice. The site Investigator may withdraw study drug from a subject in the study in the event of intercurrent illness, adverse events, other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation, non-compliance, protocol violation or other administrative reasons. Premature withdrawal will be implemented in the case of emergency disclosure of drug treatment.

In the event of premature withdrawal from the study, the Premature Withdrawal (PW) Visit procedures and evaluations should be completed whether or not the withdrawal is determined at a regularly scheduled study visit or at an unscheduled visit.

Reasons for withdrawal of the subject prior to completion of the study must be stated in the CRF and in the site source documentation for all study subjects who were enrolled in the study. ***The CTCC must be informed within 24 hours of all study subjects who are withdrawn due to an adverse event.***

List the following at each visit

a. Each activity to be completed by the subject and by the Investigator/staff at each visit and any instructions that the subject is to follow between visits.

b. If special investigations are to be performed or if special training will be done, describe the methods, who is to perform them, and any special training needed. Provide these descriptions in Section 6, an appendix or the Operations Manual.

c. The data to be recorded, clinical samples to be collected, and materials to be issued and/or collected.

Study protocols will incorporate, if appropriate, a follow-up visit or telephone contact after the subject has finished participation in the study. State that at this site visit/contact any adverse events occurring since the subject's participation in the study ended will be recorded. Indicate that, in addition, any adverse events that were unresolved at the final study visit will be followed up.

Specify the timing of any follow-up visit/contact (this will depend on the duration of action of the study drug) and the activities which will or may need to be completed. Specify the period of time after study completion an investigator must report a serious adverse event to the CTCC.

5.12. e.g., Permanent Discontinuation of Study Drug (Early Discontinuation of Study Drug)

Subjects who permanently discontinue study drug but choose to remain in the study off drug will be seen according to their original study visit schedule but will not have [INSERT ACTIVITIES THAT WILL NO LONGER BE CONDUCTED GIVEN SUBJECT'S OFF-DRUG STATUS]. If the permanent discontinuation of study drug is not determined at a regularly scheduled study visit, the subject should be seen for an unscheduled visit and complete [LIST PROCEDURES AND EVALUATIONS].

6. ASSESSMENTS

6.1. Primary and Secondary Variables

List the primary and secondary efficacy and safety variables to be assessed by the subject and/or parent, Investigator/staff, and/or values provided by a laboratory.

Assure that the specifications of primary and secondary variables mentioned here agree with those stated in the Statistical Methods section.

6.2. Efficacy Assessments

Describe the assessments that will be performed to evaluate efficacy. Each assessment should be described in a separate subsection (e.g., 6.2.1, 6.2.2, etc.). State what the assessment involves and when it will be made (i.e., at what visits). The description should clearly state whether the site Investigator, Coordinator or Subject would perform the assessment.

Describe fully (or cite published reference) the rating scales to be used by the Investigator and/or Coordinator to quantify symptoms and signs and any special precautions to be taken.

If the subject is asked to describe symptoms, specify the rating scales to be used by the subject to quantify symptoms and signs, how the subject is to be trained to make and record these assessments and how subject compliance is to be checked. Describe any special precautions that need to be taken.

Describe any special procedures in detail that will be performed, (e.g., CT scans). If anyone other than the investigator will be responsible for evaluation of clinical outcomes, the person or group should be identified and procedures, including means of maintaining the blind, described fully. (The full procedure may be provided in an appendix or the Operations Manual.)

When specific equipment is required, state that the same piece of apparatus should be used throughout the study. Instructions on the use of the apparatus may be provided in an appendix or the Operations Manual. Describe what should happen if a change in apparatus becomes necessary.
Describe any standards (instructions) which should be followed, e.g., Unified Parkinson's Disease Rating Scale (UPDRS). A full explanation of the use of these may be provided in an appendix or the Operations Manual.

6.3. Safety Assessments

Describe the assessments that will be performed to evaluate safety. Each assessment should be described in a separate subsection (e.g., 6.3.1, 6.3.2, etc.). State what the assessment involves and when it will be made (i.e., at what visits).

Describe any special procedures in detail that will be performed, (e.g., EEGs). If anyone other than the investigator will be responsible for evaluation of clinical outcomes, e.g., review of ECGs, EEGs, blood level determinations, the person or group should be identified and procedures, including means of maintaining the blind, described fully. (The full procedure may be provided in an appendix or the Operations Manual).

When specific equipment is required, state that the same piece of apparatus should be used throughout the study. Instructions on the use of the apparatus may be provided in an appendix or the Operations Manual. Describe what should happen if a change in apparatus becomes necessary.
Describe any standards (instructions) which should be followed. A full explanation of the use of these may be provided in an appendix or the Operations Manual.

Subsections will typically include (but are not limited to):

6.3.1. Medical History & Physical/Neurological Examination

6.3.2. Vital Signs/Weight/Height

6.3.3. Clinical Laboratory Tests

(Shaded: Recommended Wording)

Clinical laboratory tests will be performed by the laboratory(ies) specified in Section 4 of the Form FDA 1572 for the study [OR NAME LABORATORY] and their reference ranges will be used. [SPONSOR] and the CTCC must be notified during the study of any changes to the reference ranges. If a clinical laboratory not listed on the Form FDA 1572 is used, their reference ranges must be provided to [SPONSOR] and the CTCC.

List the laboratory tests (and specific analytes) that will be performed and, where applicable, any special

requirements, e.g., time of day, days of study, relation to meals, time limit for sample to be tested, etc.

For non-routine tests, specify when they will be performed and what method(s) will be used.

State that all samples for laboratory analysis must be collected, prepared, labeled, and shipped according to the laboratory's requirements.

6.3.4. Electrocardiogram (ECG) (Shaded: Recommended Wording)

A 12-lead resting ECG will be performed at the [INSERT] visit. Results will be based upon the site Investigator's (or a cardiologist's) interpretation provided by the standard machine readings.

The decision as to who will interpret the ECG findings will be determined by the sponsor and study steering committee.

6.4. Other Assessments

Describe other assessments that will be conducted that may not directly relate to efficacy and safety assessments, but may apply to inclusion/exclusion eligibility or other criteria. Each assessment should be described in a separate subsection (e.g., 6.4.1, 6.4.2, etc.). State what the assessment involves and when it will be made (i.e., at what visits). Also describe any inclusion/exclusion subject eligibility criteria that would apply to each assessment.

Examples of assessments include (but are not limited to): Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI), Hoehn & Yahr Scale.
Describe any special procedures in detail that will be performed. If anyone other than the Investigator will be responsible for evaluation of clinical outcomes, the person or group should be identified and procedures, including means of maintaining the blind, described fully. (The full procedure may be provided in an appendix or the Operations Manual.)

When specific equipment is required, state that the same piece of apparatus should be used throughout the study. Instructions on the use of the apparatus may be provided in an appendix or the

Operations Manual. Describe what should happen if a change in apparatus becomes necessary.

Describe any standards (instructions) which should be followed, e.g., Mini-Mental Status Examination (MMSE). A full explanation of the use of these may be provided in an appendix or the Operations Manual.

6.5. Assessment of Subject Compliance
(Shaded: Recommended Wording)

At each study visit, the site Investigator and/or Study Coordinator will assess the subject's compliance with the study requirements. This will include checks of protocol compliance, concomitant medication use, diary card data, and use of study drug in order to assess the reliability of subject-generated data. Subjects who fail to comply with the study requirements may be withdrawn from the study.

Add information regarding assessments of plasma levels of study drug (if applicable).

7. CONCOMITANT MEDICATIONS

7.1. Required Therapy (only include if applicable to study)

State, where appropriate, the dosage, frequency, and duration of each treatment the subject is required to take in addition to trial treatments.

7.2. Allowed Concomitant Medications (Shaded: Recommended Wording)

Define the concomitant medications allowed during the study, the circumstances in which they may be used, the dosages permitted, and the duration of use.

Describe, if appropriate, when concomitant medication should be taken in relation to the study drug.

All concomitant medications must be used in accordance with approved labeling and as prescribed.

7.3. Disallowed Medications (Shaded: Recommended Wording)

Provide a list of medications that the subject should not take before or during the study and indicate any other restrictions on use.

The use of any disallowed medication should be documented.

8. STUDY DRUG ADMINISTRATION/ASSIGNMENT

8.1. Study Drug

List all study drug (including placebo) and indicate who will supply, package and label them.

List all ingredients and the formulation of the active study drug(s) and placebo (where applicable).

Describe the presentation of study drug, in terms of appearance, packaging, and labeling.

8.2. Pharmacist Instructions (only include if applicable to study)

If applicable, a brief description of the Pharmacist's responsibilities during the study should be described here, noting specifically if the pharmacist is the unblinded third party.

8.3. Storage (Shaded: Recommended Wording)

All study drug and study-supplied concomitant medication must be kept in a secure, safe area under recommended storage conditions as stated on the labeling with access limited to persons directly involved in the study.

8.4. Accountability of Study Drug Supplies (Shaded: Recommended Wording)

The site Investigator, Study Coordinator, or Pharmacist must maintain accurate records (including dates) of all supplies received from [SPONSOR] or the CTCC. All study drug supplies issued to, used by, and returned by each subject must be recorded on a Drug Log completed by the Investigator, Study Coordinator, or Pharmacist. All remaining study supplies (opened or unopened) and all sealed and unsealed code envelopes must be returned to [SPONSOR] or the University of Rochester Biostatistics Center at the conclusion of the study.

8.5. Subject Number Assignment/Enrollment

(Shaded: Recommended Wording)

All subjects will be assigned a 4-digit Subject ID Number by the site. Study drug will be pre-coded by [SPONSOR] or the CTCC with Enrollment ID/randomization kit numbers (based on the randomization plan generated by the [INSERT SPONSOR or Biostatistics Center]). Pre-assigned drug kits will be supplied to the site Investigator.

- The treatment for each subject will be assigned by a randomized code. A blocked randomization scheme will be used to ensure approximately even distribution of subjects in treatment groups at each site.

- As the subject qualifies for the randomized phase of the study, the site Investigator or Study Coordinator notifies the CTCC, who will assign to that subject an Enrollment ID (Randomization Kit) Number. These numbers are assigned in a randomized order, rather than sequentially.

- The randomization algorithm and subject enrollment process will be implemented through the Internet accessible Electronic Data Capture (EDC) system using authenticated, password-protected accounts for each study site. The EDC system will automatically validate inclusion/exclusion criteria and generate visit windows.

- Once the online enrollment process is completed, the module will print a report, and the site will receive an Enrollment Verification Report that the subject has been randomized. The report will also note the Enrollment ID Number that was assigned that corresponds to the drug kit number. If a site's EDC system is not operating, the site may alternatively call the CTCC for subject enrollment during designated working hours.

- An Enrollment Verification Report will be available to print, listing the dates for each upcoming scheduled study visit.

- Once a subject has been allocated an Enrollment ID Number these numbers cannot be assigned to another subject.

Details of the randomization which prejudice the blinding of the study, e.g., block length, must not be contained in the main study protocol.

If a study is not utilizing the Electronic Data Capture (EDC) system, the CTCC must be notified by telephone of each subject's enrollment. A CTCC staff member will use an on-line computer module during the call to record the enrollment. An Enrollment Verification Report listing the visit schedule will be faxed or e-mailed to the site after the enrollment call. This report should be filed in the participants CRF. (A full explanation of this procedure can be described in the CTCC's Operation's Manual.)

8.6. CODING/EMERGENCY DRUG DISCLOSURE

(Shaded: Recommended Wording; include only if applicable to study)

The Investigator or site Pharmacist (if applicable) will be given a sealed envelope containing a set of individual sealed envelopes or double-concealed labels will be on the drug kits, each containing the drug code for each subject. All sealed code envelopes will be returned to the [INSERT SPONSOR or Biostatistics Center] at the conclusion of the study, where they will be inspected to ensure that they have not been opened. An individual subject's envelope or label should be opened only in the case of a medical emergency. If such action is required, the CTCC must be notified first, if circumstances permit, rather than disclosing the randomization. If a drug disclosure is made, a record must be made by the Investigator/Pharmacist detailing the purpose, date and personnel involved.

Neither premature withdrawal from the study nor most clinical emergencies necessitate disclosure of treatment assignment. Most emergency situations can be handled by withdrawing study drug without disclosure of treatment assignment. However, in rare circumstances under which knowledge of the drug assignment is necessary for the treatment of a serious adverse event, site Investigators must discuss the situation with the CTCC Clinical Monitor before deciding whether or not to disclose treatment assignment. If disclosure of individual treatment assignment is undertaken it must be made by the Investigator responsible for the care of the involved subject (or by the Coordinator or other physician as designated by the Investigator). The subject will be withdrawn from further exposure to study medication. The disclosure envelope and contents should be sent to the [INSERT SPONSOR or Biostatistics Center] within [INSERT, i.e., 48] hours of the disclosure. Assigned drug treatment must not be revealed to other study staff, CTCC staff or to individuals who are not involved

directly in the clinical care of the subject unless disclosure to him/her is critical to the care of the subject.

State where and how additional copies of the code will be issued.

8.7. Dosage of Study Drug

State the dosage for all test medications. Describe provisions for the following (as applicable): Dosage initiation titration schedules, dose forgotten, dosage reduction (for AEs), and dosage suspension.

8.8. Concomitant Medications Supplied by [Sponsor]

List the name and dosage of all concomitant medications supplied by the [SPONSOR] or the CTCC.

Indicate that these supplies should be stored per the manufacturer's directions.

9. INTERCURRENT ILLNESS (Shaded: Recommended Wording)

In the event of an intercurrent illness and at the discretion of the investigator, the subject may be continued in the study with study drug treatment. The clinical course of the intercurrent illness will be followed to its appropriate conclusion and full notation made in the Case Report Forms (CRFs).

All intercurrent illnesses must be recorded in the CRFs as adverse events.

Additional information may be required by [SPONSOR] for serious adverse events.

10. SUBJECT WITHDRAWALS/DROPOUTS
(Shaded: Recommended Wording)

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's/[SPONSOR's]/ CTCC's discretion at any time.

If a subject who has started study drug terminates the study prematurely, every effort should be made to obtain final laboratory tests and evaluations of clinical status. Reasonable effort should be made to contact any subject lost to follow-up during the course of the study in order to complete study related assessments and retrieve any

outstanding data, drugs or clinical supplies. Following unsuccessful telephone contact, an effort to contact the subject by mail using a method that provides proof of receipt, should be attempted. Such efforts should be documented in the source documents.

Add a statement addressing whether subjects withdrawn from the study will be replaced.

A subject may withdraw or be withdrawn from the study for the following reasons:

- Administrative

1. Subject withdrew consent
2. [SPONSOR] or CTCC requested subject to be withdrawn
3. Request of primary care physician
4. Non-compliance
5. Failure to meet entry criteria
6. Pregnancy
7. Protocol deviation
8. Lost to follow-up/failure to return
9. Early termination of study
10. Other

- Adverse Experience

1. Worsening of the disease under study
2. Worsening of pre-existing disease (other than disease under study)
3. Intercurrent illness
4. Death
5. Major/clinically significant alteration in laboratory values after beginning study drug
6. Other adverse event

- Efficacy

1. No change in disease under study
2. Improvement in disease under study

Subject early discontinuation of study drug, study withdrawals and/or dropouts should be reported to the CTCC within 24 hours.

Screening Projection forms must be completed for all study subjects who sign informed consent. This includes subjects who completed the study or withdrew/were withdrawn from study treatment or were screened and

signed a consent form but did not start treatment. Conclusion of Study Participation forms should be completed on all subjects who have been randomized. If a subject withdraws due to an adverse event, the site must ensure that the event is captured on the CRF adverse event form.

11. SAFETY/ADVERSE EXPERIENCES

11.1. Adverse Experience (AE) Definition
(Shaded: Recommended Wording)

An adverse experience is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

Some examples of adverse experiences are:

- A change, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition.
- A deterioration in the subject's condition due to the subject's primary disease or a pre-existing condition.
- Development of an intercurrent illness during the study.
- Development of symptoms which may or may not be related to the use of a concomitant medication or study drug.
- Appearance of abnormal laboratory results or significant shifts from baseline, but still within the reference ranges, following treatment with the study drug, which the Investigator considers clinically important.

11.2. Serious Adverse Experiences (SAE)
(Shaded: Recommended Wording)

A serious adverse drug experience is defined as any adverse experience that occurs at any dose that results in any of the following outcomes:

- death;
- a life-threatening adverse experience;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity; or
- a congenital anomaly/birth defect.

An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include (but are not limited to) allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

This category also includes any event the site Investigator or the CTCC Clinical Monitor judges to be serious or which would suggest a significant hazard, contraindication, side effect or precaution. It can also involve the withdrawal of a subject from a study due to abnormal lab values, excluding screening labs.

Reports of serious adverse experiences, as defined above, require immediate notification (within 24 hours of the site's awareness) to the CTCC Project Manager or Clinical Monitor whether or not the Investigator believes that the experience is related to study drug or expected.

11.3. Recording of Adverse Experiences (Shaded: Recommended Wording)

At each subject visit the site study staff will assess adverse experiences by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last visit.

All adverse experiences, whether observed by the Investigator, elicited from or volunteered by the subject, or reported on subject diary cards, should be recorded on the CRF Adverse Event Log. This will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, contributing factors, and any action taken with respect to the study drug.

This recording will commence with the institution of protocol-specific procedures and continue until (insert the time specified by the protocol).

A specific time period, e.g., 1 month, after a subject completes a clinical trial shall be stipulated for reporting new Serious Adverse

Experiences (SAEs) and resolving AEs ongoing at the time of the last site visit on the AE CRF page. This time period will depend on the study drug, condition under treatment, duration of the study, severity, and clinical significance of the experience. Once this time period is expired, all further resolution information will be collected from the Investigator on the Adverse Experience Follow-up Form as per SOP CC-007 Safety Monitoring.

FOR ADVERSE EXPERIENCES: The Adverse Event Log CRF must be completed and be signed by the Investigator. This will include information on any action taken as a result of the adverse experience and the Investigator's opinion of the possible relationship between the experience and the study drug or participation in the study.

FOR SERIOUS ADVERSE EXPERIENCES: The Investigator must fill out the sponsor-specific serious adverse experience (SAE) Notification Form provided by the Sponsor and fax it to the CTCC. If none is provided by the Sponsor, the CTCC Serious Adverse Experience Notification (SAEN) Form or MedWatch Form (see SOP CC-007) must be completed in addition to the Adverse Event Log CRF. This will include: an identification that serious experience criteria have been met; a detailed description of the experience and other relevant information; the current status of the experience; if the subject has died, the date of death and autopsy report, if available; and the Investigator's current opinion of the relationship between the experience and the study drug/participation in the study.

11.3.1. Adverse Experience Causality Definitions
(Shaded: Recommended Wording)

For each adverse experience, the relationship to the study drug must be recorded as one of the following on the Adverse Event Log:

TERM	DEFINITION	CLARIFICATION
Unrelated	No possible relationship	The temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible.
Unlikely	Not reasonably related, although a causal relationship	While the temporal relationship between drug exposure and the adverse event onset/course does not

TERM	DEFINITION	CLARIFICATION
	cannot be ruled out	preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug.
Possibly	Causal relationship is uncertain	The temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, dechallenge or rechallenge information is either unknown or equivocal, and while other potential causes may not exist, a causal relationship to the study drug does not appear probable.
Probably	High degree of certainty for causal relationship	The temporal relationship between drug exposure and the adverse event onset/course is reasonable. There is a clinically compatible response to dechallenge (rechallenge is not required), and other causes have been eliminated or are unlikely.
Definite	Causal relationship is certain	The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

11.3.2. Adverse Event Severity Definitions
(Shaded: Recommended Wording)

The severity of each adverse experience must be recorded as one of the following on the Adverse Event Log:

MILD	No limitation of usual activities
MODERATE	Some limitation of usual activities
SEVERE	Inability to carry out usual activities

11.4. Responsibilities of Investigator/Sponsor/CTCC for Reporting Serious Adverse Experiences
(Shaded: Recommended Wording)

- The Investigator should record all serious adverse experiences that occur during the study period on the Adverse Event Log and in the appropriate source documents.

- Study Period: For the purposes of reporting serious adverse experiences, the study period is defined as the time period from when the subject signs the informed consent until [INSERT TIME, i.e., one month] following discontinuation of the study drug or the subject's completion of the study.

- The Investigator should notify the CTCC Project Manager (PM) by telephone within 24 hours of his/her becoming aware of the occurrence of a serious adverse experience. The PM will in turn notify the CTCC Clinical Monitor. The site Coordinator will fill out the [INSERT as appropriate to study: Sponsor's Serious Experience Notification Form, CTCC SAEN form or MedWatch form] provided by the CTCC, and fax it to the CTCC Project Manager (preferably prior to calling the CTCC). The designated reporting form [Sponsor or CTCC provided Serious Adverse Experience Notification Form (SAEN) or MedWatch Form] must be completed for all Serious Adverse Experiences regardless of causality or expectedness.

- Upon completion of the telephone report, the CTCC Project Manager will enter the appropriate subject information into the Incident Module. (Refer to SOP CC-007 Safety Monitoring.)

- The following information should be supplied if available at the time of the telephone call: study number, site number, subject number, subject age and gender, the study phase during which the event occurred, test treatment start date, whether the test treatment has been discontinued, date of randomization, open-label dates, date of onset of event, event description, whether event required treatment, death and autopsy report, an identification of which criteria for a serious experience have been met, the Investigator's current opinion of the relationship between the event and the study drug or study participation.

- The Investigator will comply with his/her local Institutional Review Board (IRB) regulations regarding the reporting of adverse experiences.

- The Investigator will determine with the CTCC Project Manager the date and mechanism for providing a copy of the subject's

appropriate information to the CTCC and will ensure that the information is fully completed by the agreed date.

11.5. Follow-Up of Unresolved Experiences
(Shaded: Recommended Wording)

- All serious adverse experience information will be followed until resolution or an appropriate end point is reached.

- The site Investigator and CTCC Clinical Monitor will assist the Sponsor, as appropriate, by providing further information on the event especially if the event has not resolved or stabilized at the time of completion of the Serious Adverse Experience Notification Form. This may involve contacting other clinicians responsible for the subject's care to obtain information on diagnoses, investigations performed and treatment given.

- All serious experiences occurring between the institution of protocol specific procedures (i.e., when the subject signs the informed consent) and the follow-up (*visit or telephone call*) must be recorded, reported and followed up by the site Investigator using the above procedure. If the site Investigator is made aware of the development of <u>cancer</u> in any study subject at any time after participation in the study, this should be reported to the CTCC.

11.6. Emergency Actions (Shaded: Recommended Wording)

Supply information on the known or predicted effects of overdosage with the study drug, and of known adverse effects or drug interactions, where necessary. Suggest what actions should be taken to counteract effects, if known.

State that full information is available in the Investigator's Brochure.

Also see Section 8.6 (Coding/Emergency Drug Disclosure).

11.7. Report Events

The following incidents will be considered reportable events and will be reported to the CTCC within 24 hours of the event, or the Site Investigator's knowledge of the event.

- Temporary suspension of Study Drug;
- Study Drug reduction/rechallenge;

- Subject withdrawal;
- Early discontinuation of Study Drug;
- Serious adverse event (SAE);
- Emergency treatment disclosure;
- Overdosage;
- Pregnancy;
- (Others as applicable)

12. STATISTICAL ANALYSIS

12.1. Sample Size Determination

Provide the planned sample size and the basis for it, i.e., statistical considerations and/or practical limitations.

Provide the formula for sample size and power calculations together with a reference source, if necessary. State assumptions used in the calculations, e.g., variance, size of effect to be detected, Type I and Type II error probabilities, and provide explanations as to how they were obtained, where appropriate.

12.2. Pre-Treatment Group Characteristics

Provide details concerning the methods of analysis of pre-trial subject characteristics including demographic and baseline characteristics as well as other factors that could affect responses.

State, for multicenter studies, whether comparability of treatment groups will be assessed within and across centers.

12.3. Efficacy Analysis

State the primary and secondary efficacy variables and associated statistical hypotheses.

Identify any planned reasons for excluding from the analysis subjects for whom data are available, e.g., creating an “efficacy” subset or any subgroups that are to be examined separately.

The following should be briefly addressed if applicable:

specific statistical methods used, nominal levels of significance, direction of statistical tests (one-tailed or two-tailed), variables being analyzed (e.g., means over particular time periods), handling

of missing data, interim analyses, issues arising from covariate adjustment, issues related to multicenter studies, issues related to multiple endpoints, issues arising from age and gender, and details concerning derived variables.

12.4. Treatment Failures, Non-Compliance, and Withdrawals

State how data from treatment failures, non-compliance (protocol violations), and withdrawals will be handled in the analysis.

12.5. Safety Analysis (Shaded: Recommended Wording)

12.5.1. Adverse Experiences

Adverse experience information collected at study visits will be summarized with the use of the [dictionary]. All subjects known to have received study treatment will be included in the safety analysis. At a minimum, individual report information will be displayed and adverse experience rates tabulated for each treatment group.

12.5.2. Clinical Laboratory Data

Present the current standard methods of tabulating and analyzing clinical laboratory information.

12.5.3. Other

(This section allows for the inclusion of other variables such as vital signs, ECGs, etc.)

13. REFERENCES

Provide any references referred to in the protocol.

PART B - GOOD CLINICAL PRACTICE/ADMINISTRATION

14. REGULATORY/ETHICS

14.1. Compliance Statement
(Shaded: Recommended Wording)

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA), and any applicable national and local regulations including FDA regulations under 21 CFR Parts 11, 50, 54, 56, 312 and 314.

All procedures not described in this protocol will be performed according to the study Operations Manual unless otherwise stated. Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the central laboratory manual unless otherwise stated.

14.2. Informed Consent (Shaded: Recommended Wording)

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. [SPONSOR] and the CTCC must be given an opportunity to review the consent form prior to site IRB submission and before it is used in the study.

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read and/or explained to each subject. Each subject will sign such an informed consent form or give oral consent/proxy. The subject must be assured of the freedom to withdraw from participation in the study at any time.

In the case of minors, informed consent (permission) must be obtained from the minor's parent or legal guardian. Assent (affirmative agreement to participate in research) by children will be obtained as required per 21 CFR Part 50.55.

It is the Investigator's responsibility to make sure that the subject and/or parent or legal guardian understands what she/he is agreeing to and that written informed consent is obtained before the subject is involved in any protocol-defined procedures including screening procedures. It is also the Investigator's

responsibility to retain the original signed consent form and provide each subject with a copy of the signed consent form. (Refer to SOP CC-001 Informed Consent for further details.)

14.3. Institutional Review Board/Independent Ethics Committee (Shaded: Recommended Wording)

[SPONSOR] and the CTCC will supply all necessary information to the Investigator for submission of the protocol and consent form to the IRB/IEC for review and approval. The Investigator agrees to provide the IRB/IEC all appropriate material. The trial will not begin until the Investigator has obtained appropriate IRB/IEC approval. A copy of the approval letter and approved consent form must be submitted to [SPONSOR] and the CTCC.

The Investigator will request from the IRB/IEC a composition of the IRB members reviewing the protocol and informed consent. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/IEC and [SPONSOR] and the CTCC in accordance with institutional and government regulations. The CTCC will notify the site when the IRB/IEC may be notified of study completion. It is the Investigator's responsibility to notify the IRB when the study ends. This includes study discontinuation, whether it is permanent or temporary. A copy of the site IRB/IEC's acknowledgement of study completion must be submitted to the CTCC.

The Investigator will discuss any proposed protocol changes with the CTCC Project Manager and no modifications will be made without prior written approval by CTCC and [SPONSOR], except where clinical judgment requires an immediate change for reasons of subject welfare. The IRB will be informed of any amendments to the protocol or consent form, and approval, where and when appropriate, will be obtained before implementation.

14.4. Protocol Amendments (Shaded: Recommended Wording)

Changes to the protocol should only be made via an approved protocol amendment. Protocol amendments must be approved by the Sponsor, the study's Steering Committee and each respective site's IRB/IEC prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of subjects. (See Investigator's Agreement.)

14.5. Subject Confidentiality (Shaded: Recommended Wording)

The site Investigator must assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional privacy obligations to study subjects under the Health Insurance Portability and Accountability Act (HIPAA). Subjects will be identified by code numbers on case report forms and other documents submitted to the Sponsor and the CTCC.

After a subject signs an informed consent, it is required that the site Investigator permit the study monitor, independent auditor or regulatory agency personnel to review the signed informed consent(s) and that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is in the study, and autopsy reports for deaths occurring during the study (when available).

The subject's Authorization allows the Sponsor and CTCC to receive and review the subjects' protected health information that may be re-disclosed to any authorized representative of the Sponsor, CTCC or central laboratory facility for review of subject medical records in the context of the study.

15. DOCUMENTATION

15.1. Study File and Site Documents (Shaded: Recommended Wording)

The Investigator should have the following study documents accessible to the Monitor during the study.

i. Signed Form FDA 1572
ii. *Curriculum vitae* for investigator and staff listed on Form FDA 1572
iii. The signed IRB/IEC form/letter stating IRB/IEC approval of protocol, consent forms, and advertisement notices, documentation of the IRB/IEC composition, and all IRB/IEC correspondence including notification/approval of protocol amendments, notification of serious adverse events to the IRB/IEC, and IRB/IEC notification of study termination
iv. IRB/IEC approved consent form (sample) and advertisement
v. Signed protocol (and amendments, where applicable)
vi. Signed subject consent forms
vii. Copies of the completed CRF worksheets (and subject diary cards, if applicable)

viii. Authorization log (Log of Investigators, Study Staff and Staff Related Duties) with names, signatures, initials and functional role of all persons completing protocol assessments, providing back-up to the site Investigator and Coordinator, if applicable, as well as staff entering data to the eRT system.
ix. Copies of laboratory reports/printouts (*if applicable*)
x. Any source data/records not kept with the subject's hospital/medical records
xi. Drug Accountability Log
xii. Laboratory accreditation and relevant laboratory reference ranges (*if applicable)*
xiii. Signed and dated receipt of supplies
xiv. Record of all monitoring visits made by [SPONSOR] personnel (optional)
xv. Copies of correspondence to and from [SPONSOR] and CTCC
xvi. Investigator's Brochure (where applicable)
xvii. Certificate for Human Subject Protection Program (HSPP) for each individual named on the Authorization log who have direct subject contact
xviii. Copy of professional licensure/registration, as applicable, for each individual named on the Authorization log, who has direct subject contact ensuring licensure is in the state in which the study will be conducted
xix. A Note to File indicating the assessments that will be considered source documents
xx. Any other documentation as required by the CTCC (e.g., Conflict-of-Interest/Financial Disclosure)

The Investigator must also retain all printouts/reports of tests/procedures, as specified in the protocol, for each subject.
This documentation, together with the subject's hospital/medical records, is the subject's SOURCE DATA for the study.

15.2. Maintenance and Retention of Records
(Shaded: Recommended Wording)

It is the responsibility of the site Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Investigators will be instructed to retain all study records required by [SPONSOR] and the federal regulations in a secure and safe facility with limited access for one of the following time periods based on notification from [SPONSOR] and/or CTCC.

Regulations require retention for:

- A period of at least two years after notification from the Sponsor that a U.S. NDA (New Drug Application) has been approved for the indication that was investigated.

- Or if no NDA is filed or approved for such indication, a period of at least two years after the investigation is completed or discontinued and the FDA (Food and Drug Administration) has been notified by the Sponsor.

The Investigator will be instructed to consult with [SPONSOR] and/or CTCC before disposal of any study records and to notify [SPONSOR] and/or CTCC of any change in the location, disposition, or custody of the study files.

Electronic Records: *[for studies utilizing EDC]*
An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study (see Sections 15.5 and 17.3). At the conclusion of the study a PDF (portable document format) file depicting the eCRFs for each site will be provided on electronic media for record keeping. In the event of an audit or regulatory authority inspection, the eCRFs can be printed out.

15.3. QA Audits/Site Visits (Shaded: Recommended Wording)

During the course of the study and after it has been completed it is likely that one or more study site visits will be undertaken by authorized representatives of the Sponsor or CTCC.

The purpose of the audit is to determine whether or not the study is being, or has been, conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent regulatory authority inspection.

If such audits are to occur, they will be arranged for a reasonable and agreed time.

15.4. Regulatory Inspections (Shaded: Recommended Wording)

The study may be inspected by regulatory agencies, such as the Food and Drug Administration (FDA). These inspections may take place at any time during or after the study and are based on the local regulations as well as ICH guidelines.

15.5. Data Management (Shaded: Recommended Wording)

[If utilizing Electronic Data Capture (EDC)] An Internet accessible Electronic Data Capture (EDC) system for data management will be utilized for this study. This system is protected by 128-bit server certificates and utilizes authenticated, password-protected accounts for each site. The EDC system is designed to ensure timeliness and accuracy of data as well as the prompt reporting of data from the study on an ongoing basis to the study principal and co-investigators. The system is compliant with relevant FDA regulatory requirements per 21 CFR Part 11.

The University of Rochester's Biostatistics Center *[or SPONSOR if appropriate]* will be responsible for design of the randomization scheme, creation of analytical databases, and the statistical analysis plan. Data management staff at the CTCC will be responsible for all data collection procedures.

[If utilizing Electronic Data Capture (EDC)] Data review, coding and query processing will be done through interaction with the CTCC, site personnel and the Study Monitor. Queries will be generated in real-time as the data is entered. Once the data are submitted to the EDC system, it is immediately stored in the central study database located at the CTCC and are accessible for review by data management staff. Any changes to the data will be fully captured in an electronic audit trail. As data recorded by sites in eCRFs are received, narrative text of adverse experiences and concomitant medications will be periodically coded using established coding mechanisms.

[If utilizing Electronic Data Capture (EDC)] The cycle of electronic data entry, review, query identification/resolution, and correction occurs over the course of the study period until all subjects have completed the study.

[If utilizing a "paper" system] Data collected by the Study Monitor during monitoring visits will be forwarded to the CTCC. During the period when the data is being reviewed, entered into the database, validated, and analyzed, it will be stored and maintained within the CTCC Data Management Center.

[If utilizing a "paper" system] Corrections should be made by the site personnel listed on the Site Signature Log by drawing a single line through the incorrect entry and be accompanied with the correct entry. The correction must be initialed and dated by the

site personnel making the correction. Data queries will be resolved through interaction with the CTCC, the Study Monitor and site personnel.

Data will be securely transferred to the Biostatistics Center. Once the Biostatistics Center and the CTCC, in conjunction with the Sponsor and the principal investigator, agree that all queries have been adequately resolved and the database has been deemed "clean", the database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) the database are removed at this time.

All site personnel, Sponsor and CTCC staff will remain blinded as to treatment assignments until the conclusion of the entire study. The treatment assignments are not part of the CTCC electronic database. A designated unblinded programmer and unblinded statistician in the Biostatistics Center will have access to the treatment assignments, and these individuals will not communicate about study-related matters to any other staff involved in the study. The study code will be broken by the study-responsible statistician after all outstanding substantive data queries have been resolved.

16. INVESTIGATOR/SITE (Shaded: Recommended Wording)

This study will be conducted under the supervision and direction of the Investigator(s) listed in Section 1 of the Form FDA 1572. Subinvestigators are listed in Section 6 of the Form FDA 1572. The study will be conducted at the address(es) listed in Section 3 of the Form FDA 1572.

Clinical supplies will be sent to the address listed in Section 3 of the Form FDA 1572 unless a different address is specified to [SPONSOR/CTCC] by the Investigator.

The Investigator must not conduct the study at any sites other than the one(s) stated on the Form FDA 1572.

The protocol, informed consent form, and advertisement notices will be approved by the IRB listed in Section 5 of the Form FDA 1572.

Each site Investigator is responsible for providing copies of the protocol and all other information relating to the preclinical and prior clinical experience, which were furnished to him/her, to all physicians and other study personnel responsible to them who participate in this study. The site Investigator will discuss this information with them to assure that

they are adequately informed regarding the study drug and conduct of the study. The site Investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities.

17. STUDY MONITORING (Shaded: Recommended Wording)

List the name(s) of all CTCC monitor(s):

17.1. CTCC Monitoring Staff

CTCC personnel with primary responsibility for this study are:

Clinical Monitor:

Project Manager:

If either the Clinical Monitor or Project Manager change, the CTCC will inform the Sponsor and investigator in writing.

All aspects of the study will be monitored by authorized individuals in compliance with Good Clinical Practice (GCP) and applicable regulations. The Monitors will review, on a regular basis, the progress of the study with the investigator and other site personnel.

17.2. Study Committees

17.2.1. Steering Committee

The Steering Committee (SC) is composed of the Principal and Co-Principal Investigators, Biostatistician, Director of the CTCC, Clinical Monitor, and independent investigator members of the [INSERT] Study Group with expertise in [INSERT] disease. The SC is responsible, along with the Sponsor, for the design of the study protocol and analysis plan, and oversees the clinical trial from conception to analysis and publication.

17.2.2. Data Safety Monitoring Board

[Include information as appropriate.] An independent Data Safety Monitoring Board (DSMB) will be appointed that will be responsible for periodic review of the data related to adverse events throughout the trial. The frequency

and format of the DSMB meetings, reports, and guidelines for interim analysis *[if applicable]* will be established prior to study subject enrollment.

17.3. Case Report Forms

[If utilizing a "paper" system] CRFs will be supplied by [SPONSOR/CTCC] for recording all data for each subject. It is the Investigator's responsibility to ensure that these are properly, legibly and fully completed and signed where appropriate. The CRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore the CRFs must be completed for each subject screened or enrolled according to the subject's source data on a per-visit basis. ***Data should be entered into to the CRF within [INSERT, e.g., 2 business] days of a subject's visit, and mailed to the CTCC within [INSERT, e.g., 7] business days.***

When the study is complete, a designated page of each subject's CRFs must be signed by the Investigator listed on the Form FDA 1572 to attest that it is an accurate and complete record.

[If utilizing Electronic Data Capture (EDC)] Sites will enter subject information and data into an electronic case report form (eCRF) in the Electronic Data Capture (EDC) application. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore the eCRFs must be completed for each subject screened or enrolled according to the subject's source data on a per-visit basis. Authorized study personnel will each be granted access to the electronic data capture tool via provision of a unique password-protected user-ID that will limit access to enter and view data specifically for subjects enrolled at their site. ***Data should be entered into the EDC system within [INSERT, e.g., 2 business] days of a subject's visit.***

Sites will be supplied with a set of source document worksheets that correspond to the electronic case report form (eCRF). The worksheets will serve as source documents and are required to be used to enter data into the eCRFs. Sites will initially enter all data into the subject's medical chart and/or onto source documentation worksheets prior to entering data into the eCRFs via computer stations connected remotely to the central server through an Internet browser.

<u>Electronic Signatures</u>:
An electronic signature from the site Investigator is required on the following eCRFs:

- Signature Form
- Adverse Event Form
- Adverse Event Follow-up Log
- *[Add others as appropriate, e.g., some studies may require sign off on specific components of the UHDRS or UPDRS]*

An electronic signature from the site Coordinator is required on the following eCRF:

- Signature Form

It is the site Investigator's responsibility to ensure that entries are proper and complete. During entry of data, error checks will be performed by the EDC that will immediately flag problematic data (i.e., missing, out of range, inconsistent) allowing for sites to correct the data at that time. Error checks will be implemented in the EDC based upon specifications defined in the data management plan.

The data entered from the eCRFs will be securely transmitted to a central database stored on a secure server located at the CTCC. Upon completion of a subject's visit or the study, sites have the option to print the completed eCRFs depicting the data that were entered.

Paper-based study forms (CRF worksheets) will be available from the CTCC as back-up documents in the event that the EDC system is not functioning.

At the conclusion of the study, the site will be provided with a PDF (portable document format) file on electronic media depicting eCRFs for their site. The PDF file should be printed for each subject participating in the study and filed in the subject's binder.

17.4. Monitoring Visits

To ensure compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements, the monitor or representative is responsible for monitoring that sites conduct the study according to the protocol, standard operating procedures, and other written instructions and regulatory guidelines.

Monitoring visits by a Study Monitor will be arranged in advance, at a mutually-acceptable time, with site personnel. The site

personnel must allow sufficient time for the Study Monitor to review CRFs and relevant source documents and queries. The site Coordinator and/or Investigator(s) should be available to answer questions or resolve data clarifications.

17.5. Primary Source Documents

The Investigator must maintain primary source documents supporting significant data for each subject in the subject's medical notes. These documents, which are considered 'source data', should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's consent to participant in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the Investigator(s), occurrence (or lack) of adverse events, and changes in medication usage including the date the study drug commenced and completed
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible adverse experiences
- Original, signed informed consent forms for study participation

The Investigator must also retain all subject specific printouts/reports of tests/procedures performed as a requirement of the study (e.g., laboratory and ECG reports). Laboratory reports from the central laboratory will be signed and dated by the Investigator following review and filed with the subject's source documents. This documentation, together with the subject's hospital/site medical records, is the subject's 'source data' for the study. During monitoring visits the Study Monitor will need to validate data in the CRFs against these source data.

The CTCC in concert with the Sponsor will provide sample source document forms (optional).

[If utilizing Electronic Data Capture (EDC)]
CRF Worksheets

Sites will be supplied with a set of worksheets that correspond to the electronic case report form (eCRF) for this study. The worksheets will serve as source documents for study observations and assessments and should be used to enter data into the eCRF. Additional source documentation for information not specifically included on the source document may be recorded on a separate document.

The following worksheets based on the eCRFs will be considered source documents for this study:
[List as appropriate]

[If utilizing a "paper" system]
The following case report forms (CRFs) will be considered source documents for this study:
(List as appropriate]

17.6. Closeout Visit (Shaded: Recommended Wording)

Following the completion of the study, Study Monitor(s) will conduct a closeout visit to ensure that all data queries have been resolved, any protocol deviations are documented appropriately, all relevant study data has been retrieved, that study drug and clinical supplies have been/will be properly returned to [SPONSOR] and that the Investigator has copies of all study-related data/information on file.