Human and animal behavioural change with nonapeptide agonists and antagonists

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IND APPLICATION DRAFT:

CLINICAL STUDY PROTOCOL

Safety and efficacy of V1/V3 Manning peptide

CLINICAL PROTOCOL: Summary Information

Clinical Protocol Title:

Safety and efficacy of V1/V3 Manning peptide in alcohol abuse in men.
Safety and efficacy of V1/V3 Manning peptide in heroin abuse in men.
Safety and efficacy of V1/V3 Manning peptide in fever in men.
Safety and efficacy of V1/V3 Manning peptide in anorgasmy in females.
Safety and efficacy of V1/V3 Manning peptide in autism in men.
Safety and efficacy of V1/V3 Manning peptide in aggressive behavior in men.
Safety and efficacy of V1/V3 Manning peptide in pain/hyperalgesia in men.
Safety and efficacy of V1/V3 Manning peptide in veterinary use: promote animal reproduction.

Protocol number: *(Incorporate only if applicable)*

Version number and date:

Number protocol amendments (i.e., revised clinical protocols) consecutively and include the date of the amendment.

Phase of clinical investigation:

Phase 1-2 clinical investigations.

IND number:

"Pending".

Investigational drug(s):

Specify the assigned name and/or, when applicable, the code number of the investigational drug(s).

Sponsor:

Incorporate sponsor-investigator's name
Incorporate sponsor-investigator's academic department
Incorporate the mailing address:

Authorized Signatories: *(Incorporate only if applicable)*

Incorporate the name(s) and title(s) of individual(s) authorized to sign the Form FDA 1571 submissions on behalf of the Sponsor of the IND application.

Study Monitor:

Incorporate the following, as written

XXX for Human Subject Research

Medical Director: *(Incorporate only if applicable)*

If the Sponsor of the IND application is not a physician (or dentist, if applicable), incorporate the name, title, address, and telephone number of the qualified physician (or dentist, if applicable) who is responsible for all medical (or dental) decisions related to the clinical research study.

Investigator(s):

Incorporate the name(s) and title(s) of the investigator(s) who is (are) responsible for conducting the clinical research study, and the address and telephone number of the study site(s). For sponsor-investigator IND applications, the identity of the Investigator should be the same as the identity of the Sponsor.

Clinical Laboratory(ies), Technical Department(s), and Institution(s) Providing Clinical Study Services:

Incorporate the names and addresses of the clinical laboratory(ies), hospital(s), and other medical and/or technical departments or entities that will be utilized for the conduct of the clinical research study.

C. Clinical Protocol

1. Introduction:

1.1 Background:

Name and/or identity (i.e. chemical composition) of the investigational drug product(s):
V1/V3 antagonist Manning- peptide:

X=D-Tyr-Phe-Val-Asn-Arg-Pro-Arg-Arg-NH2

Disease or condition for which the investigational drug product is being evaluated:
- alcohol abuse in men
- heroin abuse in men
- fever in men
- anorgasmy in females
- autism in men
- aggressive behavior in men
- pain/hyperalgesia in men
- veterinary use: promote animal reproduction .

Detailed discussion of the current status of the disease or condition (i.e., clinical indication) for which the investigational drug is being evaluated under this IND application; to include current problems or deficiencies that warrant an evaluation of the investigational drug.

1.2 Rationale:

Summarize the reason(s) why it is felt that the investigational drug(s) will be safe and effective for the clinical indication for which it is being evaluated under this IND application; i.e.:

Summarize the safety and efficacy findings from non-clinical (i.e., animal or in-vitro) studies that support the evaluation of the investigational drug(s) in humans.

The results of several prior clinical research studies of the investigational drug(s) that are relevant to the proposed clinical evaluation of the investigational drug(s) under this IND application was summarized beforehand.

Summarize any existing information related to the human pharmacokinetics of the investigational drug.

Summarize any existing information related to the human safety profile (including known potential risks) of the investigational drug.

Several existing information related to the effectiveness of the investigational drug for the clinical indication for which it is being evaluated under this IND application was collected and presented and summarized beforehand.

Since the investigational drug is a nonapeptide, the proposed route of administration is intravenous, subcutaneous or nasal spray.
The dosage, dosage regimen, and duration of dosing of the investigational drug should be specified. Since there seems to be a particular dose-dependency on the effect of the drug, investigation of the dosing is especially important in this study.

Summary the nature of the individuals (e.g., age range, sex, disease state or underlying condition) who will be included in the proposed clinical evaluation of the investigational drug.

- *alcohol abuse in me: alcoholists*
- *heroin abuse in men: heroinists*
- *fever in men: unmanagable fever*
- *anorgasmy in females: females with anorgasmy or oligoorgasmy*
- *autism in men: autists*
- *aggressive behavior in men: healthy people with experimentally induced aggression*
- *pain/hyperalgesia in men: people with chronic pain*
- *veterinary use: promote animal reproduction: pandas, sheeps, cows, horses*

To our knowledge) the investigational drug has not been withdrawn from research or marketing in any country for any reason related to its safety or effectiveness.

2. Clinical Study Objectives:

2.1 Primary objective:

The primary objective and specific aim of the proposed clinical evaluation of the investigational drug for Phase 1 and 2 clinical research studies is an evaluation of the safety of the investigational drug.

2.2 Secondary objectives:

The secondary objectives and specific aims of the proposed clinical evaluation of the investigational drugs is PoC (proof of concept) and dose-finding.

3. Study Design:

Type/design 1 of the proposed clinical evaluation of the investigational drug in human subjects: double-blind, placebo-controlled, parallel design

Type/design 2 of the proposed clinical evaluation of the investigational drug in animals: open-label, placebo-controlled, parallel design

- *Randomization, blinding (in Type/design 2) will be taken to minimize/avoid bias on the part of the study participants,, investigators, and analysts;*

- *the expected total duration of subject participation and a general description of the sequence and duration of individual study periods or stages (including follow-up, if any) will be determined according to the specific study objectives.*

3.1 Study design schematic

A schematic diagram of the study design and stages will be provided according to the specific study objectives.

3.2 Allocation to treatment *(Incorporate only if the proposed clinical study involves multiple treatment arms)*

Description of the plan and procedures for allocating the study participants to the various cohorts or arms of the proposed clinical investigation of the investigational drug will depend on the specific study aims.

3.3 Breaking the blind

The blind should be broken if a given study participant suffer a serious adverse event wherein knowledge of the identity of the study drug received by the subject is necessary for effective emergency treatment of the event. Description of the detailed procedures will depend on the specific study aims.

4. Subject Selection:

Specify the location where the proposed clinical evaluation of the investigational drug will be conducted.
The estimated total number of individuals/animals to be enrolled into this clinical/animal research study will be determined according to the specific study aims.
No formal sample size determination will be used in Phase I clinical studies/animal studies.
In Phase II clinical studies/animal studies sample size determinations will be made on the basis of the results of the Phase I clinical studies and other available information.
The "enrollment into the study" in human clinical studies will be defined as providing informed consent for study participation.

4.1 Subject inclusion criteria

List the specific subject inclusion criteria will be given according to the specific research goals.

4.2 Subject exclusion criteria

List the specific subject exclusion criteria will be given according to the specific research goals.

5. Study Drug(s):

Describe, in detail, the study drugs that will be administered to each cohort or arm of the proposed clinical evaluation of the investigational drug; to include, for each drug product, its identity (i.e., proprietary name), FDA-approval status, dose (including maximum dose), dosing schedule, route/mode of administration, and duration of administration.

Describe, if applicable, the procedures for dose reductions or increases based on the outcome of safety or efficacy assessments; or, if applicable, the procedures for the tapering of doses upon subject withdrawal from, or completion of, the clinical research study.

5.1 Study drug compliance/adherence

5.1.1 Withdrawal of subjects due to non-compliance/ adherence

Specification of the criteria and procedures for withdrawing research subjects from study participation due to non-compliance/adherence

with the assigned study dosage regimen, the clinical research study procedures, or the instructions of the investigator or members of the investigator's research staff will be dependent on the specific aims of the study.

Specification if subjects withdrawn from study participation due to noncompliance/adherence will be replaced and, if so, the corresponding procedures for their replacement will be dependent on the specific aims of the study.

5.2 Study drug supplies

5.2.1 Formulation and packaging

Description of the source and formulation of the study drug (investigational drug and placebo or comparator drug) and how they will be packaged and labeled for use in the clinical/animal research study will be dependent on the specific aims of the study.

5.2.2 Preparing and dispensing

Description of the procedures for the on-site preparation, if applicable, and dispensing of the study drug should be made according to the specific study goals.

5.2.3 Drug administration

The description of the procedures (e.g., investigator-directed, research subject-directed) for the administration of the study drug; to include, if applicable, the specific instructions that will be provided to the research subjects will be dependent on the specific aims of the study.

5.4 Study drug storage and accountability

Description of the requirements (e.g., temperature, protection from light) for appropriate storage of the study drug so as to ensure their stability throughout the assigned expiration period will be made depending on the specific aims, route of administration etc. of the study.

Description of the procedures for ensuring proper accountability of each of the study drugs; to include the procedures for destruction or other disposition of the study drugs upon completion or termination of the clinical research study will be dependent on the specific aims and technical realization of the study.

5.5 Concomitant Medications

Description or list of the concomitant medications that will be permitted and/or not permitted prior to and/or during the subject's participation in the clinical research study will be dependent on the specific aims of the study.

Description of how the subjects' use of concomitant medications will be assessed and accounted for during clinical study participation will be dependent on the specific aims of the study.

5.5.2 Rescue Medication

Identification, if applicable, of acceptable rescue medications that may be used by the subjects during their participation in the clinical study will be dependent on the specific aims of the study.

6. Research Study Procedures:

6.1 Screening procedures

Detailed description or listing of the procedures that will be performed at subject screening to verify subject eligibility for study participation will be dependent on the specific aims of the study.

6.2 Study drug procedures

Detailed description or listing of the procedures that will be performed for, and in association with, the administration of the study drugs will be dependent on the specific aims of the study.

6.3 Follow-up procedures *(Incorporate only if follow-up procedures will be performed)*

Detailed description or listing of the follow-up procedures that will be performed after the subject completes the study drug administration procedures will be dependent on the specific aims of the study.

6.4 Schedule of activities (Study Table)

Provision of a table that summarizes the clinical protocol procedures; to include the procedures that will be performed at screening, during the study drug administration, and at follow-up (if applicable) to the study drug administration will be dependent on the specific aims of the study.

7. Safety and Effectiveness Assessments:

7.2 Safety assessments

Specification of the parameters (i.e., procedures, laboratory tests, or other measures) that will be used to evaluate the safety of the study treatment(s); to include the methods and timing for assessing, recording, and analyzing these parameters will be dependent on the specific aims of the study.

7.2 Effectiveness assessments

Specification of the parameters (i.e., observations and/or measurements) that will be used to evaluate the effectiveness of the study drug(s); to include the methods and timing for assessing, recording, and analyzing these parameters will be dependent on the specific aims of the study.

8. Adverse Event Reporting:

8.1 Adverse event definitions

Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Adverse reaction means any adverse event caused by a drug.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction"

- *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Serious, suspected adverse reaction. A suspected adverse reaction is considered "serious" if, in the view of the Investigator (i.e., the study site

principal investigator) or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

- Important drug-related medical events that may not result in death, be life-threatening, or require hospitalization may be considered "serious" when, based upon appropriate medical judgment, they may jeopardize the research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in the 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.

  Unexpected, suspected adverse reaction. A suspected adverse reaction is considered "unexpected" if it is not listed in the general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

8.2 Recording/Reporting requirements

8.2.1 Eliciting adverse event information

Addressing of the frequency and process for eliciting adverse event information from research subjects; e.g., "Research subjects will be routinely questioned about adverse events at study visits." will be dependent on the specific aims of the study.

8.2.2 Recording requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

Adverse events or abnormal test findings felt to be associated with the study drug(s) will be followed until the event (or its sequelae) or the

abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

8.2.2.1 Abnormal test findings

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
    - Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the Sponsor-Investigator of the IND application

8.2.2.2 Causality and severity assessment

The Sponsor-Investigator of the IND application will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s); and 3) if the adverse event meets the criteria for a *serious adverse event*.

If the Sponsor-Investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s)", the adverse event will be classified as *associated with the use of the study drug(s)* for reporting purposes. If the Sponsor-Investigator's final determination of causality is "unknown but not related to the study drug(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

8.3 Reporting of adverse reactions

8.3.1 Reporting of adverse reactions to the FDA

8.3.1.1 Written IND Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500 A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a *serious and unexpected, suspected adverse reaction*. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

8.3.1.2 Telephoned IND Safety Reports – Fatal or life-threatening suspected adverse reactions

<u>In addition to the subsequent submission of a written IND Safety Report</u> (i.e., completed FDA Form 3500A), the Sponsor-Investigator

will notify the responsible review division of the FDA by telephone or facsimile transmission of any *unexpected, fatal or life-threatening suspected adverse reaction.*

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

8.3.2 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

8.4 Withdrawal of subjects due to adverse events

Specification of the criteria and procedures for withdrawing subjects from continued receipt of the study drug(s) due to an observed or volunteered adverse event will be dependent on the specific aims of the study.

Addressing of the criteria that will be used to define the severity of adverse events will be dependent on the specific aims of the study.

Addressing of the nature and timing of any data that will continue to be collected from the withdrawn subjects will be dependent on the specific aims of the study.

Specification of whether subjects withdrawn from study participation due to an adverse event will be replaced and, if so, the corresponding procedures for their replacement will be dependent on the specific aims of the study.

9. Statistical Methods/Data Analysis:

9.1 Study endpoints

9.1.1 Primary endpoint(s)

Specification of the primary endpoint(s) to be measured during the clinical study will be dependent on the specific aims of the study.

For PoC computer-intensive exact tests will be used with a multiplicity adjustment with the Bonferroni-Holm procedure. This procedure is based on ordering the p-values from the smallest to the largest.

For dose-finding Bayesian escalation with overdose control using a Bayesian logistic regression model (EWOC) will be used. *Bayesian methods formalize a learning process, where models begin with initial estimates of model parameters based on prior pre-clinical or clinical data, and models are then updated with new information as it becomes available. This updated information forms the basis of dose escalation. With Bayesian logistic regression MTD can be found in such a way that precision of model estimates are incorporated into dosing decisions, and restriction of the chance of exposing patients to excessive toxicity, whilst allowing clinicians to make informed dosing decisions based on estimated probabilities of under-dosing and targeted-dosing. When using the EWOC model, one needs to specify intervals to summarize the probability of DLT.*

Alternatively, another useful method for the design and analysis of dose-finding Studies is the MCP-Mod procedure, which is a combination of a multiple comparison procedure (MCP) and modeling (Mod). The starting point of the MCP-Mod method is the recognition of the fact that the power of a dose-response trend test depends on the unknown dose-response curve. Tukey et al (1985) proposed the use of several transformations f of the predictor variable dose and then to use the minimum multiplicity adjusted p-value to decide for or against a significant trend. Therefore, the MCP-Mod procedure starts by defining

a set of candidate models M covering a suitable range of dose-response shapes. Tukey proposed the use of the following transformations at the initial step:
arithmetic scaling: $(fd_i)=d_i$,
ordinal scaling: $(fd_i)=i$,
logarithmic scaling: $(fd_i)=logd_i)$,
arithmetic-logarithmic scaling: $(fd_i)=d_i$, if i=1, and $(fd_i)=logd_i)$ otherwise.
Then the lowest p-value is taken and compared – after an appropriate multiplicity adjustment – compared to the familywise error rate (FWER) α.
Bretz et al. (2005) formalized this approach and extended it in several ways, with parametrically modeling the dose response relationship for a response Y in the following form:
$Y_{ij} = f(d_i, \theta) + e_{ij}$, *where* $e_{ij} \sim N(0, \sigma)$.

Dose-finding is a trade-off between efficacy and safety. Since the ultimate goal of finding the best dose can not always be fully reached even with a series of experiments, dose-finding should be seen as a scientific process instead of viewing it as a single clinical trial.

The dose-finding process usually begins with in vitro and in vivo preclinical experiments, which may lead to a determination of a toxicology limit for humans. The first-in-man (FIM) phase I clinical trial conducted among healthy volunteers start with a dose well below a dose expected to give a pharmacodynamic effect. Then the dose can be increased to a level of toxicology limit based on preclinical data. If a tolerability limit is reached in FIM (observed tolerability problems), then the highest dose without these problems usually determines the upper limit for the doses for further trials.

9.1.2 Secondary endpoints

Specification of the secondary endpoint(s), if any, to be measured during the clinical study will be dependent on the specific aims of the study.

9.2 Sample size determination

In the Phase I Studies no formal sample size determination will be made, i.e. no formal determination of the number of subjects planned to be enrolled into the clinical/animal study because of lack of enough information and the primary goals of the study, i.e. in first in men studies only a few patients/people/animals will be included for assessing the safety profile of the drug.
In Phase II studies formal sample size calculations will be made for PoC (proof of concept) and dose-finding based on available data.

In Phase II studies significance level (alpha) 0.05 and power 0.80 will be used for study/clinical justification.

9.3 Definition(s): Analysis population(s)

Definition of Safety Population, Intent to Treat Population, Modified Intent to Treat Population corresponding to the analysis populations that will be utilized in the statistical evaluation of study endpoints will be dependent on the specific aims of the study.

9.4 Effectiveness analysis

Description of the analysis populations and statistical methods that will be employed in the analysis (analyses) of primary and secondary endpoints related to evaluations of the effectiveness of the study drugs will be dependent on the particular study aims. The level of significance to be used is 0.05 and the power is 0.80.
Sample size calculations are different in various trial types, but there are common elements. In a classical clinical trial a hypothesis is referred to an assumption or statement about a population regarding the efficacy and safety of the drug investigated. For testing the hypotheses of interest, a random sample is drawn from the population to evaluate the hypotheses about the drug. A statistical test is then performed to determine whether the so-called null hypothesis can be rejected at a given significance level or not. The selection of hypotheses depends on the study objectives. Sample size for a clinical trial is affected by the type of the problem investigated as well as level of measurement[1] of the variable studied, type of estimated difference between two populations, variability, power and significance level. An increase in power, decrease in significant level, decrease of the estimated difference, or increase in variability will result in an increase in sample size. In a superiority trial the larger the difference, the smaller the sample size and vice versa.

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment and/or in the final report submitted to the IND application.

9.5 Safety analysis

Description of the analysis population(s) and statistical methods that will be employed in the analysis of the safety of the study drugs will be dependent on the particular study aims.
The level of significance to be used is 0.10.

[1] Stevens, S. S. On the theory of scales and measurement. Science, New Series, Vol. 103, No. 2864 (Jun 7, 1946) pp. 677-680.; http://web.duke.edu/philosophy/bio/Papers/Stevens_Measurement.pdf

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment and/or in the final report submitted to the IND application.

9.6 Interim analysis

No interim analysis will be used in the planned study/studies.

Any deviations from the previously described statistical plans based on the results of the interim analysis will be described and justified in a protocol amendment and/or in the final report submitted to the IND application.

9.7 Data and Safety Monitoring Committee

Description of the composition and operations of the Data and Safety Monitoring Committee that will provide oversight of the clinical study will be dependent on the particular study.

The process for communication of Data and Safety Monitoring Committee determinations to the Sponsor-Investigator will be dependent on the particular study.

10. Quality Control and Quality Assurance:

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff (similar to a Human Subject Research Conduct and Compliance Office) to be recruited.

The Sponsor-Investigator will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

The nature and timing of the quality control/quality assurance reviews (i.e., independent of the previously described monitoring activities) that will be undertaken by the Sponsor-Investigator to ensure appropriate conduct of the clinical research study and quality and completeness of the accrued study data will be dependent on the particular study. Details will be described in a data and safety monitoring plan for the proposed clinical research study.

11. Data Handling and Record-Keeping:

11.1 Data recording/Case Report Forms

A Case Report Form (CRF, presented in Appendix 1 according to the given study goals) will be completed for each subject enrolled into the clinical study. The Sponsor-Investigator will review, approve and sign/date each completed CRF; the Sponsor-Investigator's signature serving as attestation of the Sponsor-Investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

Identification of any clinical study data that will be recorded directly on the CRF, whereupon the CRF data is to be considered the Source Data.

Procedures for accounting for any missed, unused, and/or spurious data: Index cases and proband contacts with missing data on important predictors will be excluded from analyses. In the main study, we will use multiple imputation with 10 imputed datasets to replace missing values on outcome and predictor variables. If 10 imputed datasets are not sufficient to ensure stability of estimates we will use 20 imputed datasets. Multiple imputation makes maximum use of available data and maximizes statistical power while requiring less strict theoretical assumptions than to a complete case analysis, or single imputation of mean values. We note that this is now one of the preferred (and standard) methods for analyzing clinical trials data.

Description of how the subject-specific data and Case Report Forms will be coded and how these materials, and the subject identification code list, will be stored so as to protect the subjects' confidentiality will be dependent on the particular study. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

If an electronic system will be used as the sole instrument for the recording and analysis of clinical and laboratory data related to the safety and/or effectiveness of the study drug(s), compliance with the FDA's electronic records and electronic signatures regulations at 21 CFR Part 11 will be made.

(Note that in the absence of any qualifying statement, the FDA will assume that the electronic data recording system is compliant with these FDA regulations. Hence, if the electronic data system being used has not been certified to be in compliance with the 21 CFR Part 11, incorporate a statement specifying such; e.g. "The electronic data recording data system being used for this clinical research study has not been fully certified as being compliant with the FDA regulations at 21 CFR Part 11 due to the limited scope of this clinical research study.")

11.2 Record maintenance and retention

The Sponsor-Investigator will maintain records in accordance with Good Clinical Practice guidelines; to include:

- FDA correspondence related to the IND and clinical protocol, including copies of submitted Safety Reports and Annual Reports
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Signed FDA Form 1572 Statements of Investigator (i.e., for the Sponsor-Investigator)
- Financial disclosure information (i.e., for the Sponsor-Investigator and for sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the research study data])
- Curriculum vitae (i.e., for the Sponsor-Investigator)
- Certificates of required training; e.g., human subject protections, Good Clinical Practice, etc. (i.e., for the Sponsor-Investigator and for all sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Listing of printed names/signatures. (i.e., for the Sponsor-Investigator and for all sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Laboratory certification information

- Instructions for on-site preparation and handling of the investigational drug(s), study treatment(s), and other study-related materials (i.e., if not addressed in the clinical protocol)
- Responsibility delegation log
- Signed informed consent forms
- Completed Case Report Forms; signed and dated by Sponsor-Investigator
- Source Documents or certified copies of Source Documents
- Monitoring visit reports
- Copies of Sponsor-Investigator correspondence (including notifications of safety information) to sub-investigators
- Subject screening and enrollment logs
- Subject identification code list
- Investigational drug accountability records, including documentation of drug disposal.
- Final clinical study report

- Decoding procedures for blinded trials
- Master randomization list
- Retained biological specimen log
- Interim data analysis report(s)

- Signed FDA Form 1572 Statements of Investigator (i.e. for Investigators responsible for the conduct of the clinical research study at external study sites).
- Financial disclosure information (i.e., for Investigators responsible for the conduct of the clinical research study at external study sites; also for all study site sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Curriculum vitae (i.e., for Investigators responsible for the conduct of the clinical research study at external study sites)
- Certificates of required training; e.g., human subject protections, Good Clinical Practice, etc. (i.e., for Investigators responsible for the conduct of the clinical research study at external study sites; also for all study site sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Listing of printed names/signatures (i.e., for Investigators responsible for the conduct of the clinical research study at external study sites; also for all study site sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Copies of initial and continuing IRB approval notifications (i.e., for each of the external study sites)

- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol (i.e., for each of the external study sites)
- Laboratory certification information (i.e., for each of the external study sites)
- Monitoring visit reports (i.e., for all external study sites)
- Copies of Sponsor-Investigator correspondence (including notifications of safety information) to Investigators responsible for the conduct of the clinical research study at external study sites

The Sponsor-Investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

12. Ethics:

12.1 Institutional Review Board (IRB) approval

Incorporate the following, as written

The Sponsor-Investigator will obtain, from the Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Sponsor-Investigator will promptly notify the IRB of the deviation.

The Sponsor IRB (Institutional Review Board) operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the Spronsor IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Sponsor-Investigator's decision to modify the previously accepted clinical protocol:

- for a Phase 1 clinical study: The Sponsor-Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the Phase 1 clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol will be addressed in the Annual Report to the IND.

- for Phase 2 clinical studies: The Sponsor-Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to a Phase 2 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of Phase 2 clinical protocol changes requiring the submission of a Protocol Amendment include:

    - Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.

    - Any significant change in the design of the protocol (such as the addition or deletion of a control group).

    - The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

12.2 Ethical and scientific conduct of the clinical research study

Incorporate the following, as written

The clinical research study will be conducted in accordance with the current IRB-approved clinical protocol; ICH GCP Guidelines adopted by the FDA; and relevant policies, requirements, and regulations of the Sponsor IRB, and applicable agencies.

12.3 Subject informed consent

The Sponsor-Investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The Sponsor-Investigator, or a sub-investigator(s) designated by the Sponsor-

Investigator, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The Sponsor-Investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The Sponsor-Investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the Sponsor-Investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study

13. Study Discontinuation Criteria:

13.1 Discontinuation of individual research subjects (refer also to sections 5.1.1 and 8.4)

Any discontinuation criteria or "stopping rules" for individual research subjects that were not addressed previously under section 5.1.1 (Withdrawal of subjects due to non-compliance/adherence) or section 8.4 (Withdrawal of subjects due to adverse events) of the clinical protocol will be defined in accordance with the particular study goals.

The nature and timing of any data that will continue to be collected from the withdrawn subjects will be defined in accordance with the particular study goals.

The specification whether subjects withdrawn from study participation due to these criteria will be replaced and, if so, the corresponding procedures for their replacement will be defined in accordance with the particular study goals.

13.2 Sponsor-Investigator discontinuation of the clinical research study

Describe the discontinuation criteria or "stopping rules" for parts of the clinical research study, if applicable, or for the entire clinical research study.

The specification of the respective protocol modifications that will be submitted prospectively to the Sponsor IRB and to the FDA for discontinuation of parts of the clinical study will be defined in accordance with the particular study goals..

The specification that the Sponsor Institutional Review Board (IRB) and the FDA will be notified promptly of discontinuation of the entire clinical study will be defined in accordance with the particular study goals..

Addressing the procedures for notifying enrolled subjects and sub-investigators (and, if applicable, external study site Investigators) of discontinuation of parts of the clinical research study; and for obtaining the informed consent of the subjects for continued participation in the study will be defined in accordance with the particular study goals.

Addressing the procedures for notifying enrolled research subjects and sub-investigators (and, if applicable, external site Investigators) of discontinuation of the clinical research study; to include the types and timing of data that will be subsequently collected from the enrolled subjects to ensure their safety will be defined in accordance with the particular study goals.

14. References:

References to the literature and data that are cited in the Background, Rationale, and other applicable sections of the clinical protocol will be defined in accordance with the particular study goals.