PRINCIPAL/OVERALL INVESTIGATOR
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PROTOCOL TITLE
A randomized, double-blind, placebo-controlled, cross-over study to evaluate the efficacy of L-serine in subjects with hereditary sensory and autonomic neuropathy type 1

FUNDING
FDA Office of Orphan Product Development

VERSION DATE
February 25, 2013

SPECIFIC AIMS
Concisely state the objectives of the study and the hypothesis being tested.

The primary goal of the study is to determine whether L-serine supplementation in subjects with hereditary sensory and autonomic neuropathy type I (HSAN1) is more effective than placebo by assessing the proportion of failures following a two year study.

Secondary goals include exploring correlations between neurological function, measured by the Charcot Marie Tooth Neuropathy Score (CMTNS) and intraepidermal nerve fiber density (IENFD), which will be established by skin biopsies. In addition, valuable natural history data on HSAN1 through the placebo arm will be obtained.

BACKGROUND AND SIGNIFICANCE
Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

We recently identified two novel deoxysphingoid lipids (dSL) that accumulate in plasma of HSAN1 subjects and mutant transgenic HSAN1 mice. The disease is caused by missense mutations in the SPTLC1 gene encoding a subunit of the enzyme serine palmitoyltransferase (SPT). In normal circumstances, the SPT enzyme catalyzes the reaction of palmitoyl-CoA with serine to form sphinganine. The two newly identified dSL, deoxysphinganine and deoxymethylsphinganine, arise from condensation of palmitoyl-CoA with L-alanine and L-glycine respectively, suggesting that HSAN1 mutations alter amino acid selectivity of SPT. In support of this hypothesis, we have shown that levels of dSL in humans and mice can be lowered by supplementation with the enzyme’s normal substrate, L-serine.

Our clinical trial efforts are hampered by the fact that (1) the rate of disease progression is not established and (2) L-serine is readily available over the counter, prompting subjects to start supplementation on their own in the near future. The benefits of the current trial
design are that it will establish natural history in the placebo group and provide an incentive for subjects, as they will receive costly L-serine for free.

**RESEARCH DESIGN AND METHODS**

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, “Enrollment at Partners will be limited to adults although the sponsor’s protocol is open to both children and adults.”

In this randomized, double-blind, placebo-controlled, cross-over study, 20 research subjects with HSAN1 will be enrolled with 10 subjects assigned to L-serine (400 mg/kg/d) and 10 assigned to placebo who are each treated for 1 year, followed by cross-over to L-serine by all subjects for one additional year. Subjects will be treated with L-serine and placebo or L-serine for a total of 2 years. Subjects will be randomized to L-serine or placebo.

Neurological function (CMT Neuropathy Score, neurophysiology) will be measured at baseline and at 6 month intervals. In addition, skin biopsies will be performed to measure intra-epidermal nerve fiber density (IENFD) at baseline and at 6 month intervals. Plasma dSL levels will be evaluated every 6 months for the entirety of the study to ensure compliance with L-serine versus placebo regimen.

Time to failure will be assessed in the two groups. If a subject increases by more than one point on the CMTNS ( >1 point) during the study period, the subject will be considered a treatment failure.

Study subjects meeting all of the following criteria will be allowed to enroll in the study:

1. HSAN1 subjects with prominent sensory loss with foot ulcers or shooting pains and confirmed mutations in SPTLC1.
2. Age 18 years or older.
3. Subjects must not have taken L-serine for at least 30 days prior to randomization (L-serine-naïve subjects are permitted in the study).
4. Capable of providing informed consent and following trial procedures.
5. Women must not become pregnant for the duration of the study and must be willing to use two contraceptive therapies and have a negative pregnancy test throughout the course of the study.

Study subjects meeting any of the following criteria during screening evaluations will be excluded from entry into the study:

1. Any cause of neuropathy other than HSAN1 (such as diabetes or drug-induced neuropathy).
2. History or presence of kidney stones.
3. History or presence of poliomyelitis.
4. History or presence of radiotherapy.
5. Clinically significant history of unstable or severe cardiac, oncologic, hepatic, or renal disease, or other medically significant illness.
6. Serious illness requiring systemic treatment and/or hospitalization. Subject may enroll when he/she either completes therapy or is clinically stable on therapy, in the opinion of the site investigator, for at least 10 days prior to study entry.
7. The presence of unstable psychiatric disease, cognitive impairment, or dementia that would impair ability of the subject to provide informed consent, according to PI judgment, or a history of active substance abuse within the prior year.
8. Subjects who are non-ambulatory.
10. Subjects who are taking blood-thinners, such as warfarin (Coumadin) or heparin.
11. Women who are pregnant, breastfeeding, or not using adequate contraception. Adequate contraception includes: abstinence, hormonal contraception (oral contraception, implanted contraception, injected contraception or other hormonal (patch or contraceptive ring, for example) contraception), intrauterine device (IUD) in place for ≥ 3 months, barrier method in conjunction with spermicide, or another adequate method.

Briefly describe study procedures. Include any local site restrictions, for example, “Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study.” Describe study endpoints.

**Primary objective and endpoint:**
The primary objective of the study is to define treatment failure by utilizing the Charcot Marie Tooth Neuropathy Score (CMTNS), a 36 point functional rating scale.

**Secondary objective and endpoint:**
The secondary objectives of this study are to:

1. Measure the intraepidermal nerve fiber density (IENFD) on skin biopsy.
   - Skin biopsies to assess epidermal nerve fiber density will be obtained before treatment and at 6 month intervals. This allows a direct assessment of the number of myelinated and unmyelinated fibers while on L-serine versus placebo. The number of fibers at baseline will be compared to subsequent biopsies.

2. Measures of sensory and autonomic testing.
   - A comprehensive battery of autonomic tests will allow us to evaluate all major autonomic domains impacted by the neuropathy: cholinergic, adrenergic and sudomotor. Measures of sensory testing will allow for further comprehensive evaluation of abnormalities in thermal and vibratory sensations.

   - We will assess whether oral L-serine reduces plasma deoxysphingolipids (dSL), a proximate putative neurotoxin, and lower plasma dSL levels improve downstream measures of neuropathology.

4. Nutrition journals.
   - Dietary influences during the trial will be accounted for through the collection of nutrition journals.

5. Pharmacokinetic Samples.
   - 24-hr pharmacokinetic (PK) studies will occur at the start of the first and second year, allowing us to complete two PK series, with placebo at baseline providing information on diurnal patterns of dSL levels and an active arm at 1 year providing information on PK of L-serine on top of a stable background. As L-serine has not been regulated by the FDA, no pharmacokinetic studies on L-serine exist. This information will be crucial in deciding on the frequency of dosing in a future phase III trial.
(6) Disease questionnaires.
   - Baseline and follow-up questionnaires will be used to gather general, physical, and lifestyle information about the subjects.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

There are options for treating the symptoms of HSAN1. There is medication that can help with the pain, as well as supportive foot wear and braces that can help with walking. Subjects can talk to their primary care physicians about these options.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

To minimize adverse side effects of L-serine supplementation, participants chosen to receive L-serine will be given 400 mg/kg/d. At this dose, no side effects have been reported in previous studies.

To ease the discomfort of blood draws and biopsies, topical EMLA can be applied to the site prior to specimen acquisition.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

No dose limiting toxicity of L-serine has been observed at the dose we are using in the study (400 mg/kg/d). L-serine supplementation has been widely used in other studies. We will monitor renal and liver function as well as plasma L-serine levels. In case renal failure occurs, we assume the subject would be hospitalized and excluded from our study.

Exclusion criteria listed above are in place to protect the subjects. Although studies have shown that there are no side effects to serine supplementation in pregnant women, we are unsure of its effects on the fetus. As such, pregnant women will be excluded from this study, and women participating in this study will be using an accepted method of contraception.

Subjects actively abusing drug or alcohol will not be included, to prevent any possible side effects of mixing substances with serine.

Subjects on anticoagulants such as warfarin (Coumadin) or heparin will not be included, so that they will not lose excess blood during the biopsy procedure.

Subjects with uncontrolled diabetes are not included, as the placebo is a sugar compound, and elevated blood sugar may cause serious health conditions.

Lastly, subjects with any serious illness requiring systematic treatment and/or hospitalization will be excluded.
FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Risks of blood sample include a short amount of pain and possibly a small bruise at the spot on the skin where the needle goes into the vein. If the subject wants, we may put some EMLA cream (2.5% lidocaine cream) on the skin to make it numb before we draw blood. This will make the blood draw less uncomfortable. Occasionally, a person feels faint during the procedure. Rarely, an infection can develop, which we can easily treat with antibiotics.

Risks of biopsy include pain, bleeding, and scarring. Rarely, an infection can develop, which we can easily treat with antibiotics.

Risks of nerve conduction studies include slight discomfort from the electrical pulses. It will feel similar to a shock from static electricity, like when you touch a metal door knob in the winter.

Risks of autonomic function testing are minimal. During the tilt table testing, the subject may experience some lightheadedness or dizziness. During the sweat testing, the subject may feel a slight pinching sensation under the electrode when it dispenses the sweat stimulating medicine. This only lasts a fraction of a second.

Serine supplements have been used in other studies. Subjects in other studies have taken serine with no side effects at the dose we are using. However, there may be other risks in taking serine that are not known at this time.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, “It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects.” Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

This research study is the first drug trial to target the cause of HSAN1, but it is not known whether or not subjects will benefit from taking part in this research. Others with neurodegenerative disorders may benefit in the future from what we learn in this research study.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.
A total of 20 subjects with HSAN1 will be recruited for this clinical trial. Subjects will be randomized to receive L-serine or placebo in the first year. In the second year, all subjects will receive L-serine. Since this study aims to evaluate the efficacy of L-serine treatment in HSAN1 subjects, placebo controls are more appropriate than healthy controls. As such, the study population is representative of the population that may directly benefit from this research.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Subjects who do not speak English will not be excluded from participation in the research. We will arrange for an interpreter to be present in order to explain the consent form and use the consent forms in different languages as made available by Partners. Consent of subjects who do not speak English will be obtained and documented following the procedures outlined in the PHRC Policy.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

We will announce our study via clinicaltrials.gov and other internet websites, including disease foundation websites. We will also have brochures in the waiting room area of the MGH Neuromuscular Center. Both web announcement and brochure will contain contact information of study staff. If potential subjects are interested in joining our study, they can call our study staff. A phone script will be followed for pre-screening. If subjects are found to be eligible, we will invite them to come to MGH for a screening visit. We will also send them a copy of the informed consent document so that they can carefully read the document and discuss the research study with their family, friends, and/or physician.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available.

Travel expenses will be provided up to $500 if subjects are traveling from out-of-state. Parking at MGH (clinic visit, neurophysiology studies) will be compensated. Furthermore, they will be provided L-serine free of cost.
CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators’ own patients, describe how the potential for coercion will be avoided.

Informed Consent will be obtained from the subjects at the screening visits. Subjects are informed of the risks of participating in the study prior to enrollment during the consent review and are able to withdraw from the study at any time. The benefits and alternatives to participating in this study are also described during the consent process. Although the benefits of the study are unknown, it is hoped that L-serine will slow the rate of progression of HSAN1, and that the knowledge gained will benefit others with HSAN1 in the future. They will have adequate time to consider participation. Any potential for coercion will be avoided by the possibility of consultation with a second expert in neurometabolic disorders not involved in the study.

Confidentiality will be maintained, as all subjects will be assigned a screening ID when they give informed consent. Once eligibility of the subject has been determined and the subject is enrolled, a subject ID will be assigned. All research data will be coded using screening and subject IDs in place of subject information.

The subject files will be kept in a secure double locked area. The web based database used during the trial will be secure. It can be entered from MGH and the University of Massachusetts Medical School, Worcester. It will be located behind a secure firewall. To date, no breach of our security barriers has occurred, and we actively maintain a high level of security to assess the confidentiality of our databases. Only key personnel in this proposal will have access to the data and the codes. Subject results will never be discussed in any form in the presence of other subjects in the study or with non-laboratory personnel. Each subject will be referred by their screening and/or subject ID number only. The PI, Steering Committee, Medical Monitor, and Data Safety Monitoring Board will monitor safety and risks throughout the study. Site research pharmacists and physician drug monitor are unblinded to subject treatment assignment.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

An independent Data and Safety Monitoring Board (DSMB) has been assembled for the trial. The DSMB receives the blinded and unblinded summary reports of the frequency of all clinical adverse events and safety laboratory tests for planned periodic meetings approximately every 6 months throughout the study. Meetings may be held via teleconference at the request of the Board Members. In addition, the DSMB Chair may call ad hoc meetings.

Summaries of SAEs and enrollment will be provided approximately monthly to the DSMB by the study biostatisticians (MGH Biostatistics Department). The DSMB can ask to receive SAE reports more frequently. As necessary, the DSMB can review the frequencies of clinical and laboratory abnormalities. Recommendations for modification or termination of the trial based on safety data will be made by the DSMB to the PI and Steering Committee. The DSMB will review safety data throughout the trial and may stop the trial for safety if they determine there is a significant difference in the rate of a particular AE that would indicate a risk that is greater than the possible benefit of the study drug. A significant increase in the frequency of any AE should be examined by the DSMB although it may not lead to a recommendation by the DSMB.

Prior to each DSMB meeting, the PI will provide an update to the DSMB on enrollment, data quality (missing data), and protocol adherence. The PI will be responsible for communication with the DSMB.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners’ IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners’ IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.
NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting.

This study will utilize the MedDRA (Medical Dictionary for Regulatory Activities) coding system for adverse event recording. The Principal Investigator will carefully monitor each subject throughout the study for possible adverse events. All clinical adverse events are recorded in the Adverse Event log in the subject’s study binder. The site should fill out the Adverse Event log and enter the AE information into the EDC system within 48 hours of the site learning of a new AE. Entries on the AE log (and into the EDC) will include the following: name and severity of the event, the date of onset, the date of resolution, the relationship to study drug, action taken, and primary outcome of the event.

All AEs will be collected and reported in the EDC system and compiled into reports for periodic review by the Medical Monitor. The Medical Monitor shall promptly review all information relevant to the safety of the study drug, including all serious adverse events (SAEs). Special attention will be paid to those that result in permanent discontinuation of the investigational drug being studied, whether serious or non-serious.

Subjects will be monitored for AEs from the time they sign consent until the completion of their participation in the study (defined as death, consent withdrawal, loss to follow up, early study termination for other reasons, or following completion of the entire study). Relationship of adverse events to the experimental intervention will be assessed at each in-person and telephone study visit by recording all voluntary complaints of subjects and by assessment of the clinical features of HSAN1.

**MONITORING AND QUALITY ASSURANCE**

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

Protocol procedures are reviewed with the Principal Investigator and associated personnel prior to the study to ensure the accuracy and reliability of data. The Principal Investigator must adhere to the protocol detailed in this document and agree that any changes to the protocol must be approved by the Coordination Center prior to seeking approval from the site IRB. The Principal Investigator will be responsible for enrolling only those study subjects who have met protocol eligibility criteria.

The data will be entered by site personnel into the clinical trial database and verified for accuracy.

The Study Monitor will visit the study site at least twice annually to review source documentation materials, informed consent forms, and confirm entered data and that data queries have been accurately completed. The Study Monitor will also verify that SAEs and
protocol violations have been reported appropriately to the local IRB as required. The Study Monitor will review clinical facilities resources and procedures for evaluating study subjects and study drug dispensing. Subsequently, the Study Monitor will provide monitoring reports to the MGH Project Manager and, if requested, will provide reports of protocol compliance to the PI and the Steering Committee. Completed informed consent forms from each subject must be available in the subject’s file and verified for proper documentation. A documentation outlining the monitoring plan is provided to the Study Monitor.

For guidance, refer to the following Partners policies:
Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/datasafe.htm
Adverse Event Reporting Guidelines
http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY
Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

The original signed and dated research consent form will be retained in the subject study binder. A copy of the signed research consent form will be given to the subject. The participating subject will be assigned a screening ID until eligibility has been determined. If a subject is found to be eligible, a subject ID number will be assigned. All research records will be de-identified and entered into an electronic data capture system using subject IDs.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the subject ID to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using subject IDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor’s designee.

All local and federal guidelines and regulations regarding maintaining study subject confidentiality of data will be adhered to.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS
Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent,
and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Coded plasma samples will be sent for lipid analysis to Dr. Thorsten Hornemann at the University of Zurich. The codes will be retained as described above. Our outside collaborators will not be able to link the specimens to individual subjects.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

No specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

The skin biopsies will occur at the University of Massachusetts Medical School and processed by placing the skin tissue in Zamboni’s fixative. A courier will bring the tissue to a JCAHO certified laboratory at Massachusetts General Hospital that specializes in assessment of ENFD in human skin biopsies. The qualified physician will be blinded to sample identifiers.

REFERENCES


Penno et al. Hereditary sensory neuropathy type 1 is caused by the accumulation of two neuro-toxic sphingolipids. J Biol Chem. 2010


