Effect of neurokin-1 receptor (NK_1R) antagonism on pruritus in patients with Sézary Syndrome

A randomized, placebo-controlled, double-blinded study of aprepitant in the treatment of pruritus in patients with Sézary Syndrome

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Supported by:

(Any modification to the protocol should be annotated on the coversheet or in an appendix. The annotation should note the exact words that are changed, the location in the protocol, the date the modification was approved by the Executive Committee, and the date it became effective.)

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PRÉCIS

Study Title

Effect of neurokin-1 receptor (NK_1R) antagonism on pruritus in patients with Sézary Syndrome.

Objectives

The purpose of this study is to test the hypothesis that administration of aprepitant decreases the severity of pruritus in patients with Sézary Syndrome.

Design and Outcomes

Single center, randomized, double-blinded, placebo-controlled, crossover study design.

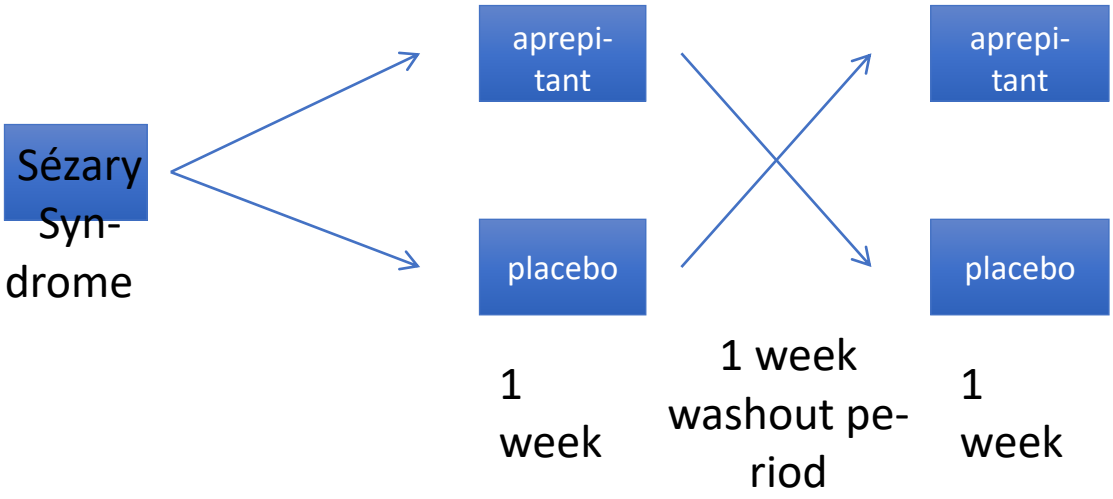
The study will examine the effect of aprepitant on pruritus in patients with Sézary Syndrome. A baseline substance P level will be obtained in each subject from the serum. Substance P will also be measured through tissue obtained through stored skin biopsies. Subjects will be randomly allocated to one of two treatments, aprepitant or placebo. Subjects will remain on the first treatment for one week. They will then undergo a washout period of one week from the first drug, and will then crossover to the other drug for a one-week period.

Pruritus will be evaluated daily by means of a visual analogue scale (VAS), in which a score of 0 indicates no pruritus and a score of 10 indicates the worst pruritus imaginable.

Quality of life will be evaluated by means of the Dermatology Life Quality Index (DLQI) questionnaire (range, 0 to 30, higher scores indicate a worse outcome).

1 Interventions and Duration

Subjects will be randomly assigned to receive aprepitant or placebo using a permuted-block randomization algorithm.



Subjects with Sézary Syndrome will be randomly allocated to receive placebo versus aprepitant. Aprepitant will be administered orally in a dose of 125mg on day 1 and 80mg daily on each subsequent day for a total of 7 days. After the 1week treatment period, all subjects will undergo a 1week washout period from study drug. Subjects will then cross-over and receive the opposite study drug, again for a 7 day period.

Subjects will undergo a baseline blood draw in order to quantify the amount of substance P in the serum. All patients with Sézary Syndrome are expected to have had their skin biopsied when originally diagnosed in the VUMC dermatology clinic, and substance P levels will be obtained through tissue from these stored skin biopsies.

Subjects will complete a VAS on the first day of treatment and daily for the duration of the study. The DLQI will be completed on the first and last day of treatment, in each treatment arm.

2 Sample Size and Population

All subjects will be patients in the Vanderbilt University Medical Center (VUMC) dermatology clinic with known Sézary Syndrome. The goal of this clinical trial is to deter-

mine if NK1R antagonism alters the severity of pruritus in Sézary Syndrome. Sample size calculations have been based on the decrease in severity of pruritus following aprepitant administration in an open-label, non-randomized study of 5 patients with cutaneous T-cell lymphoma (3 with Sézary Syndrome and 2 with mycosis fungoides) with a decrease in pruritus from 9.6 to 4.3 as measured on the visual analogue scale. In our study, a sample size of 14 will have 83% power to detect a difference in means using a paired t-test with a 0.05 two-sided significance level. Assuming 10% dropout rate, we will enroll 16 subjects.

3 Study objectives

Primary Objective

To evaluate the effect of administration of aprepitant on pruritus in patients with Sézary Syndrome compared to administration of placebo.

The primary endpoint is the severity of pruritus as measured on the VAS.
We hypothesize that administration of aprepitant will decrease the severity of pruritus in patients with Sézary Syndrome compared to administration of placebo.

The secondary endpoint is the quality of life as measured on the DLQI. We hypothesize that administration of aprepitant will lower the score on the quality of life index compared to administration of placebo.

Secondary Objective

We hypothesize that serum substance P concentrations correlate with substance P in the skin and that circulating substance P concentrations will be elevated compared to those measured in normal controls in our laboratory.

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4 Background

Sézary Syndrome, the leukemic variant in the spectrum of cutaneous T-cell lymphomas (CTCL), is characterized by erythroderma, peripheral adenopathies and circulating atypical mononuclear cells with cerebriform nuclei (Sézary cells, SC).[1] Pruritus is a common complaint in those with Sézary Syndrome and is often severe enough to cause insomnia and depression, and may impair quality of life.[2,3] Conventional peripheral acting antipruritic agents, such as emollients, topical steroids, and oral antihistamines, are ineffective, and targets for antipruritic drugs are expanding to include centrally located receptors.[2,4]

Substance P (SP) is neuropeptide of the tachykinin family. Among the three known tachykinin receptors, neurokinin-1, -2, and -3 receptors, neurokinin-1 receptor (NK_1R) has the highest affinity for SP and is broadly expressed in the peripheral and central nervous system.[4] SP is responsible for nociceptive transmission from the peripheral to the central nervous system.[5] It is also known to induce the release of inflammatory mediators from mast cells and is a potent vasodilator.[5] It has been shown that intradermally applied SP induces scratching behavior in mice, indicating a role of SP in pruritus.[4]

Lack of CD26, also known as dipeptidyl peptidase IV (DPPIV) is a constant feature of circulating SC, and levels of the CD4+ CD26- subpopulation correlate with the extent of peripheral blood involvement in Sézary Syndrome.[1] DPPIV is a cell-surface marker of T lymphocytes that plays a role in the activation and proliferation of lymphocytes.[5] DPPIV, along with angiotensin-converting enzyme (ACE), inactivates circulating SP.[5,6] DPPIV sequentially releases the two N-terminal dipeptides[7] of SP, leaving the resulting fragment active as a transmitter of sensory nerves, but lacking the capacity to stimulate histamine release from mast cells.[5,8] The breakdown of exogenous SP is decreased in DPPIV-deficient rats.[5,6] Patients with Sézary Syndrome may suffer from severe pruritus because they lack DPPIV and are unable to fully breakdown SP.

Substance P is inactivated by ACE and DPPIV. During ACE inhibition or when there is lack of DPPIV, there is less breakdown of exogenous substance P leading to increased vascular permeability through the NK_1R. Increased circulating substance P can lead to the increased release of inflammatory mediators from mast cells, resulting in increased pruritus.

5 Rationale

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors which has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK_1 receptors.

Given that patients with Sézary Syndrome lack DPPIV, an enzyme known to breakdown substance P, we hypothesize that decreased degradation of substance P can contribute to pruritus. With evidence that substance P can contribute to pruritus, it is important to establish whether NK1 receptor antagonism is effective in treating the condition.

The purpose of this randomized, double-blind, placebo-controlled study is to test the hypothesis that administration of aprepitant will decrease the severity of pruritus in patients with Sèzary Syndrome.

6 Supporting Data

Oral administration of aprepitant is FDA approved in the treatment of chemotherapy-induced nausea and vomiting and is administered in the dose of 125mg day 1 and 80mg day 2 and 3.[9] The most common adverse effects reported in phase 3 trials include fatigue, hiccups, and dyspepsia.[9]

Aprepitant has been used in case reports and small studies in the treatment of pruritus. Aprepitant as an Antipruritic Agent?[3] was case report describing the effect of aprepitant on pruritus in **3** patients with Sézary Syndrome. An oral dose of 80mg daily for one week was administered and pruritus was evaluated by means of a visual-analogue scale, in which a score of 0 indicates no pruritus and a score of 10 indicates the worst pruritus imaginable. Scores of 7, 8, and 9 dropped to 2, 3, and 2, respectively, after one day of treatment, and remained the same after one week. Evaluation of quality of life was with the Dermatology Life Quality Index (DLQI) questionnaire (range, 0 to 30; higher scores indicate worse outcomes), resulted in scores of 22 and 17, and dropped to 8 and 4, respectively, for 2 of the 3 patients, the third patient was not evaluated with this scale.

Oral Aprepitant is Highly Efficient in the Therapy of Refractory Pruritus in Erythrodermic Cutaneous T-cell Lymphoma was a small prospective, **open label** study examining the effect of aprepitant in **5** patients with erythrodermic CTCL (3 with Sèzary syndrome and 2 with erythrodermic mycosis Fungoides). Severity of pruritus was assessed using a VAS, and quality of life was measured via the DLQI. A response was defined as a more than 50% reduction, no response less than 25% and a partial response between 25% and 50% reduction of the VAS compared to baseline. The overall response rate to the aprepitant therapy was 80% with 4/5 patients demonstrating a good response.

7 Selection and enrollment of subjects

Inclusion Criteria

1. Known Sézary Syndrome – the leukemic variant in the spectrum of cutaneous T-cell lymphomas (CTCL) characterized by erythroderma, peripheral adenopathies ad circulating atypical mononuclear cells with cerebriform nuclei (Sézary Cells).
2. Pruritus uncontrolled by conventional treatment. Baseline VAS must be > 4.
3. Age 18 through 80 years of age.

Exclusion Criteria

1. Known hepatic impairment (Defined as LFTs > 3 times the upper limit of normal).
    a. LFTs will be obtained prior to drug administration.
2. Pregnancy (all women of child-bearing potential will undergo urine beta-hcg testing).
3. Aprepitant is contraindicated with concurrent use of cisapride or pimozide, and other potent inhibitors of CYP3A4.

8 Study enrollment procedures

All patients who present to the VUMC dermatology clinic, or established patients of the clinic, with biopsy proven Sèzary Syndrome will be eligible. Informed consent will be obtained verbally and in writing. Subjects who meet the inclusion and exclusion criteria will be enrolled.

Subjects will be randomly assigned to treatment using a permuted-block randomization algorithm. Dr. Chang Yu, study biostatistician, will provide an allocation schedule, which will be uploaded on a password-protected web site that is accessible to the investigational pharmacist, but not the investigators. After subjects have been consented and screened for the inclusion and exclusion criteria, investigators will document these and for the eligible subjects, fax a copy of a prescription to the investigational pharmacy. The pharmacist will assign the subject a randomization number from the central allocation schedule and will provide the investigator with the drug. An extra label containing the randomization number will be put in the subject's records.

If a subject declines to continue the study at any time, the study will be stopped and all collected data will be withdrawn and destroyed.

9 Study interventions

Interventions, Administration, and Duration

Following consent, each patient will undergo a baseline history and physical examination (targeted to skin). A prescription will be faxed to the investigational pharmacist. An intravenous catheter will be placed in the patient's forearm for blood drawing. Blood will be drawn for quantification of substance P. The severity of pruritus will be quantified using VAS (appendix). Study drug will be given orally in a dose of 125mg on day 1 and 80mg daily on each subsequent day for a total of 7 days.

Handling of Study Interventions

Study drug and matching placebo will be purchased by the investigational pharmacy (vs. will be provided by Merck & Co.) ***Need to hear back from Merck.***

Concomitant Interventions

Required Interventions: Subjects will be instructed to continue using any anti-pruritic treatments they used prior to the initiation of study.

Prohibited interventions: Apreptitant is contraindicated with concurrent use of cisapride and pimozide, and other inhibitors of CYP3A4.

10 Clinical and laboratory evaluations

See following page.

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377 ***Schedule of Evaluations***

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Evaluation	Screening	Pre-Entry (0 day)	1 day	2 day	3 day	4 day	5 day	6 day	7 day	Washout 1 week	1 day	2 day	3 day	4 day	5 day	6 day	7 day
Informed Consent	X																
Documentation of Sèzary Syndrome	X																
Medical/Treatment History		X															
Clinical Assessment		X							X		X						X
Targeted Physical Exam		X							X		X						X
Pregnancy Testing		X									X						
Complete metabolic panel		X															
CBC		X															
Urinalysis		X															
Serum substance P		X															
Visual analogue scale (VAS)		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Dermatology quality of life index (DLQI)			X						X		X						X

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Timing of Evaluations

i. Pre-Randomization Evaluations

These evaluations occur prior to the subject receiving any study interventions.

Screening
Subjects will be known patients of the VUMC dermatology clinic with known Sèzary Syndrome. After the informed consent document has been signed, documentation of their disease will be obtained.

Pre-Entry
Subjects who have successfully been screened for eligibility and have provided informed consent will return for baseline physical exam and screening labs. A medical/treatment history will be obtained. A clinical assessment with targeted skin exam will be performed. Screening labs include beta-hcg for women of child –bearing potential, complete metabolic panel, complete blood count, urinalysis, and serum substance P. A baseline VAS will be completed.

Entry
Only subjects whose labs fall within normal limits, and whose pruritus score as measured on the VAS is greater than or equal to 4 will enter the study. Subjects will be randomized to aprepitant or placebo. Subjects will be required to meet at the VUMC dermatology clinic on day 1 of the study. They will be provided with a supply of study drug, visual-analogue scales, and quality of life index scales to last them 7 days. They will return to clinic after 7 days of treatment.

ii. On-Study Evaluations

Subjects will be instructed to take the study drug each morning, days 1-7 while on the first drug treatment, and again days 1-7 for the second drug treatment. They will also be instructed to fill out a VAS each evening. They will return to the VUMC dermatology clinic on day 7 for a clinical assessment and physical exam targeted to skin. They will undergo a washout period from study drug and will then return again to the VUMC dermatology clinic. After the washout period, the subjects will crossover to receive the opposite drug treatment to which they were randomized. They will undergo a clinical assessment, targeted physical exam and pregnancy testing on day 1. They will be instructed to take study drug and complete the VAS and DLQI as specified in the first arm of the study. They will return to clinic on the final day for a clinical assessment and targeted physical exam.

iii. Intervention Discontinuation Evaluations

Each subject will undergo a clinical assessment and targeted physical exam at the end of the study.

iv. Post-Intervention Evaluations

Subjects will be instructed to call the VUMC dermatology clinic if symptoms of pruritus worsen post-study. They will not be followed for any specific outcomes after the second drug period.

v. Final Evaluations

Each subject will undergo a clinical assessment and targeted physical exam at the end of the study.

vi. Pregnancy

Female subjects will be instructed to avoid pregnancy while on-study. A pregnancy test will be completed upon entry into both study drug arms. If a subject becomes pregnant she will be removed from the study.

Special Instructions and Definitions of Evaluations

vii. Informed Consent

Informed consent will be obtained verbally and in writing. Documentation of consent will be kept in the subject's chart. A copy of the consent will be provided to the subject.

viii. Documentation of Sèzary Syndrome

Sèzary Syndrome is the leukemic variant in the spectrum of cutaneous T-cell lymphomas (CTCL) characterized by erythroderma, peripheral adenopathies ad circulating atypical mononuclear cells with cerebriform nuclei (Sézary Cells). Subjects will be known to the VUMC dermatology clinic and will have a documented diagnosis of their disease in the medical chart.

ix. Medical History

The subject's full medical history will be reviewed.

x. Treatment History

The subject's treatment history, specific to the treatment of Sèzary Syndrome, will be reviewed and documented.

xi. Clinical Assessment

The clinical assessment will focus on Sèzary Syndrome and the effect it has on the subject's level of functioning.

xii. Targeted physical exam

A physical exam targeted to a full body skin examination will be completed.

xiii. Laboratory Evaluations

Laboratory evaluations will include a complete metabolic panel (CMP), complete blood count (CBC), urinalysis, beta-hcg for women of child-bearing potential, and a serum substance P level.

xiv. Questionnaires

Pruritus will be evaluated daily by means of a VAS, in which a score of 0 indicates no pruritus and a score of 10 indicates the worst pruritus imaginable.

Quality of life will be evaluated by means of the DLQI (range, 0 to 30, higher scores indicate a worse outcome).

Off-Intervention Requirements

There are no requirements for follow-up on subjects once they have stopped using the study intervention.

11 Management of adverse experiences

An adverse event will be classified as serious if it a) results in death, b) is life-threatening, c) requires inpatient hospitalization, or prolongation of existing hospitalization, d) results in persistent or significant disability or incapacity, e) is a congenital anomaly or birth defect. Serious adverse events will be reported to the Data and Safety Monitoring Committee the IRB, NIH, and the FDA within 24 hours.

12 Criteria for intervention discontinuation

Subjects will be instructed to contact a physician associated with the study if they no longer want to continue as an enrolled subject in the study. The subject will be withdrawn from the study and all data will be destroyed.

13 Statistical considerations

General Design Issues

The primary objective is to evaluate the effect of aprepitant on pruritus in patients with Sézary Syndrome compared to administration of placebo. The study is designed as a cross-over between aprepitant and placebo. It is important that each subject receive both study treatments, as pruritus is a subjective sensation, which may be partially relieved by placebo.

The primary endpoint is a 50% reduction in pruritus as measured by the VAS. The secondary endpoint is a reduction in the DLQI score. There is no pre-defined expected reduction in the DLQI. Subjects will need to complete a VAS daily. To ensure compliance, subjects will be instructed to complete the VAS at the same time each day and will receive a phone call mid-week to ensure they are on track with the study.

The half-life of aprepitant is 9-14 hours. Using 14 hours and approximating 5 half-lives as the time needed to reach steady state, it will take 3 days to reach steady state. An intervention time of one-week will be sufficient to reach steady state and experience maximal effects of the drug. It will again take 3 days for drug washout, making a one-week washout period from study drug appropriate.

Outcomes

Primary Objective

To evaluate the effect of administration of aprepitant on pruritus in patients with Sézary Syndrome compared to administration of placebo.

The primary endpoint is the severity of pruritus as measured on the VAS.
We hypothesize that administration of aprepitant will decrease the severity of pruritus in patients with Sézary Syndrome compared to administration of placebo.

The secondary endpoint is the quality of life as measured on the DLQI. We hypothesize that administration of aprepitant will lower the score on the quality of life index compared to administration of placebo.

Secondary Objective

We hypothesize that serum substance P concentrations correlate with substance P in the skin and that circulating substance P concentrations will be elevated compared to those measured in normal controls in our laboratory.

Sample Size and Accrual

Sample size calculations were based on a paired t-test to detect a difference on the primary endpoint VAS between the placebo and aprepitant treatments. In a study conducted by Booken et al,[2] they reported a baseline VAS of 9.6 ± 0.9 (mean ± SD, n=5) and 4.3 ± 3.4 after at least 6 weeks of treatment. Based on these data and conservative assumptions of a correlation of 0.5 between two repeated measures on the same subjects and a 20% placebo effect, and assuming a treatment effect of 50% reduction (from 9.6 to 4.8), a sample size of 14 (16 need to be enrolled, assuming a 10% dropout rate) will have 83% power to detect a mean difference of 2.9 (a mean of 7.7 on placebo versus a mean of 4.8 on aprepitant), using an SD of 3.4 for the within subject difference.

Data Analyses

Standard graphing and screening techniques will be used to detect outliers and to ensure data accuracy. Summary statistics for both continuous and categorical variables will be provided by randomization groups to describe the study sample.

This study is a 2X2 crossover (aprepitant and placebo) study with repeated daily measure-

ments of visual analog scale for itching and additional secondary endpoints listed above during each study period. Treatment difference (i.e., aprepitant vs placebo) for each endpoint will be estimated as within-subject mean difference along with their 95% confidence intervals. A paired t-test will be performed to compare the responses. If normality of the data is violated, signed rank test will be used. Even though we will make every effort to minimize a carry-over effect or period effect, we will nevertheless test for these effects using the baseline measures taken right before each study period. This evaluation will be conducted using mixed-effect models and/or direct comparisons.

Mixed-effect models will also be used to analyze the data with a random subject effect and with treatment (aprepitant versus placebo) and time trend as fixed effects. We might also include baseline covariates which are potential confounders in the mixed-effect models to adjust for their effects. We will explore different plausible covariance matrices, such as compound symmetry and a first-order autoregressive process [AR(1)], in the mixed-effect models. We will check the model fitting by superimposing the fitted mean response profiles on a time plot of the average observed response and to superimpose the fitted variogram on a plot of the empirical variogram (Diggle et al. 2002). The mixed-effect model analysis for other continuous endpoints will be conducted similarly.

Based on our past experience, we anticipate a drop-out rate of 10% or less. Subjects who drop out prior to completing study period 2 will be replaced. We will also keep the period one data collected on the replaced subject. If data are missing for an isolated time point during one of the study periods, mixed-effect models are robust in the sense that they can include subjects with missing data at some time points but not all time points to estimate the effects of interest. However, we will conservatively impute missing data to perform analyses with and without missing data to corroborate our findings.

Specific inferences on effects of interest will be made by reporting a point estimate along with a 95% confidence interval and the p value. Hypotheses will be tested at the level of α=0.05. This data analysis plan will be carried out using statistical software SPSS for Windows (Version 16.0, SPSS, Chicago, IL) or SAS® release 9.1.3 (Cary, NC) or statistical analysis package R (R Development Core Team, 2007).

14 Data collection, site monitoring, and adverse experience reporting

Data and Safety Monitoring Plan

The protocols and any amendments will be reviewed and approved by the Vanderbilt Institutional Review Board before any subject is enrolled. The PI will closely oversee the protocol in conjunction with the research fellow and dedicated research nurses. Any adverse events or toxicities will be reported to the IRB as per IRB guidelines. Any untoward medical event will be classified as an adverse event, regardless of its causal relationship with the study. An adverse event will be classified as serious if it a) results in death, b) is life-threatening, c) requires inpatient hospitalization, or prolongation of exist-

ing hospitalization, d) results in persistent or significant disability or incapacity, e) is a congenital anomaly or birth defect. Serious adverse events will be reported to the IRB within 24 hours. The protocol for reporting SAEs will be standardized and reviewed at the October 2011 investigator meeting. Non-serious, unexpected adverse events will be reported within 5 working days to the DSMC and IRB.

15 Human subjects

Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject. For subjects who cannot consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

Subject Confidentiality

We will use an electronic data collection form, designed to allow direct data entry and to minimize missing and erroneous values (using the REDCap system developed in the Vanderbilt Institute for Clinical and Translational Research or VICTR). The form for the initial trial has been tested at Vanderbilt. Data will be input into a protected web-based case report form (which can be readily downloaded into an SPSS or other database spreadsheet). Expected ranges are pre-specified to prevent errors such as the shifting of decimal points. The program includes a computerized audit trail so that the identity of individuals entering or changing data can be tracked. In the case that changes are made, both original and revised data are saved. Data are backed up daily. The research nurse will enter clinical data. Brown laboratory personnel will enter research laboratory data. A unique identification case number is used to protect the confidentiality of the study participants. All research samples are bar coded with the subject's unique identifier. Data sets used for analysis also only contain this identifier. The key to the code is protected. Only the site investigator and research nurse will have access to information that identifies subjects participating in the study. The results of the tests run on research samples will not be recorded in any subject's medical record and neither the subject nor his or her doctor will be told of the results. Access to the Vanderbilt computer network is protected at the level of firewalls, TCP wrappers and university assigned user IDs. Data are secured with encryption algorithms and the network is maintained by the Medical Center's

Network Computer Service. All data will be accessible only to members of the research team.

Seven years after completion of the study, all data will be destroyed.

Follow-up and Record Retention

Records will be maintained for 7 years following the end of the study, after which time they will be destroyed.

16 Publication of research findings

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission.

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