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Feinstein Institute for Medical Research

Protocol

Nelfinavir in Systemic Lupus Erythematosus: A pilot phase IIa clinical trial

Short Title: Nelfinavir in SLE

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IND Sponsor: Meggan Mackay, MD

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PROTOCOL SYNOPSIS

Title of Protocol: Nelfinavir in Systemic Lupus Erythematosus – A Pilot Phase IIa Clinical Trial

Protocol Chair: Betty Diamond, MD

IND Holder/Sponsor Site PI: Meggan Mackay, MD

Objectives:

Primary objective: To demonstrate that the protease inhibitor nelfinavir, administered orally to SLE subjects with mild to moderately active disease, will decrease serum anti-dsDNA autoantibody binding by ≥35%.

Secondary objectives: 1) To assess the safety and tolerability of nelfinavir in SLE patients, 2) To assess the effect of nelfinavir on serum cytokine levels (IL-1, IL-6, and TNFα), 3) To assess the effect of nelfinavir on serum levels of C3, C4 and CRP, 4) To assess the effect of nelfinavir on the interferon signature, 5) To assess the effect of nelfinavir on binding of anticardiolipin antibodies, 6) To demonstrate that nelfinavir does not increase lupus disease activity and 7) To demonstrate that nelfinavir decreases disease activity.

Hypothesis:

Nelfinavir, a well-tolerated drug used to treat HIV, will be efficacious as a lupus therapeutic through inhibition of anti-dsDNA antibody binding to target organs and possibly through interfering with the formation of pro-inflammatory, DNA containing immune complexes, pro-inflammatory cytokines, and the IFN signature.

Study Arms:

A maximum of forty-three evaluable subjects will be required to assess the objective response rate (>35% reduction in dsDNA reactivity at 8 wks – end of treatment).

Stage1: (maximum of 13 subjects enrolled)

- **If 3 or fewer respond, the trial is stopped due to an inadequate response rate**
- **If 4 or more subjects respond, the trial continues to Stage 2**

Stage 2: (maximum of 30 additional subjects enrolled)

- **At end of Stage 2, if 12 or fewer of the 43 subjects respond, the treatment is declared inadequate**
- **If 13 or more respond, then the treatment will be considered for further testing**

Study Design:

This is an exploratory, multicenter, Phase IIa clinical trial with no placebo arm that utilizes the Simon Two-Stage trial design to investigate the immunomodulatory properties of nelfinavir, a protease inhibitor, in SLE patients with mild to moderate disease activity and elevated titers of anti-dsDNA antibodies. The safety, tolerability, and preliminary assessment of efficacy of nelfinavir in SLE patients will be explored.

Study Population: Subjects must meet the following criteria:

Inclusion Criteria:

1. **Subject is capable of providing written informed consent**
2. **Subject is ≥ 18 years old and ≤ 65 years old**
3. **Meets at least 4 of 11 modified American College of Rheumatology (ACR) (1997) Revised Criteria for the Classification of Systemic Lupus Erythematosus**
4. **Has mild to moderate disease activity defined as**
   - **A minimum SLEDAI score of 2 excluding points for serology (anti-dsDNA antibody and complement)**
   - **No active renal or nervous system disease**
   - **No BILAG A in any organ system**
   - **No expectation by the investigator that corticosteroids will need to be added or doses increased during the 8 week treatment period for any reason**
   - **No expectation by the investigator that immunosuppressive medication will need to be added or doses increased during the 8 week treatment period**

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5. **Has elevated titers of anti-ds DNA antibody at the time of screening (defined as the titer that meets**
   Meets criteria for "high" in the Core Laboratory at the North Shore/LIJ Health System; unequivocal high titer as opposed to borderline, indeterminate or intermediate)
6. **Has elevated titers of cross-reactive anti-DNA/DWEYS antibodies at the time of screening (the assays for anti-DNA/DWEYS antibodies will be performed in Dr. B. Diamond's laboratory; study sites will be notified of results within 3 days of receipt of the samples).**
7. If on glucocorticords, the dose must be ≤ 10mg daily and stable or decreasing 4 weeks prior to baseline
8. **If on immunosuppressive or immunomodulatory medication such as azathioprine, methotrexate, leflunomide, mycophenolate, belimumab or hydroxychloroquine, the dose must have been stable for the 3 months prior to screening, and expected to remain stable over the course of the study.**
9. **Males and females with potential for reproduction must agree to practice effective birth control measures (2 approved methods of contraception). Nelfinavir can decrease serum levels of oral contraceptives; the slightly increased risk of pregnancy due to an interaction between oral contraception and nelfinavir will be discussed when appropriate and the requirement for a second approved method of contraception will be addressed.**

Exclusion Criteria:

1. **Current or prior treatment with rituximab or anti-CD22 monoclonal antibody in the 12 months prior to this study or any other biologic agent for 90 days prior to this study**
2. **Treatment with cyclophosphamide within the 6 months prior to screening**
3. **Increase in glucocorticoid dose within 4 weeks of screening or addition of a DMARD in the three months prior to study**
4. **A history of drug or alcohol abuse within the 6 months prior to screening**
5. **Elevated LFT's:**
   - **ALT or AST ≥ 2 x upper limit of normal at screening**
   - **serum unconjugated bilirubin > 3mg/dL at screening**
6. **Dialysis or serum creatinine >1.5mg/dL**
7. **Hypercholesterolemia: total cholesterol >230 mg/dL or LDL >150 mg/dl or hypertriglyceridemia (triglyceride >200mg/dL) at screening**
8. **Laboratory/clinical evidence of: pancreatitis: amylase/lipase >3x upper limit of normal at screening**
9. **Known current/active infections including HIV, Hepatitis B, Hepatitis C**
10. **History of cancer, excluding skin cancers (squamous cell or basal cell that have been treated)**
11. **Known active tuberculosis or untreated tuberculosis**
12. **Hemoglobin < 8 g/dL**
13. **Expectation by the investigator to increase corticosteroid or immunosuppressive, or immunomodulatory medication dose at screening, baseline, or over the course of the study**
14. **Pregnancy or lactation**
15. **Consumption of > 2 cups of grapefruit juice per day**
16. **Treatment with medications metabolized using the cytochrome P3A4 pathway, such as cyclosporine, tacrolimus, gemfibrozil, niacin, itraconazole, ketoconazole, erythromycin, azithromycin, clarithromycin, bosentan, nefazodone, tricyclic antidepressants**
17. **Treatment with any drugs known to interact with nelfinavir that include amiodarone, quinidine, midazolam, triazolam, ergotamine, dihydroergotamine, methylergonovine, pimozide, lovastatin, simvastatin, rifampin, St. John's Wort, aluzosin, cisapride and sildenafil.**
18. **Any condition that, in the opinion of the Investigator, would jeopardize the subject's safety following exposure to the study drug.**

Endpoints: **Primary endpoint: inhibition of anti-dsDNA binding (based on titers from baseline to Day 56).** **Secondary endpoints: a) Safety: frequency of adverse events, b) Disease Activity: this study will evaluate the potential effect of nelfinavir on different assessments of disease activity from baseline to Day 56, including SELENA SLEDAI, BILAG, Joint count, PGA, SLICC Damage Index, Lupus PRO, patient global assessment, c) Interferon Signature: changes in expression of IFN inducible genes (from baseline to Day 56), and d) Cytokines: changes in serum cytokine levels (from baseline to day 56).**
Sample Size: A maximum of 13 subjects will be enrolled in Stage 1 and a maximum of an additional 30 subjects will be enrolled in Stage 2 for a total of 43 evaluable subjects.

INVESTIGATOR SIGNATURE PAGE

Protocol Title: Nelfinavir in SLE: A pilot phase IIa clinical trial
Protocol Version: Version 07.17.17
Study Sponsor: The Feinstein Institute for Medical Research
Funding Agency: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Please print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent to Andrew Shaw, Study Coordinator, at the Feinstein Institute for Medical Research.

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 45, 50, 56, and 312, and the International Conference on Harmonization (ICH) document "Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. Further, I will conduct the study in keeping with local, legal, and regulatory requirements.

As a Principal Investigator on this protocol, I agree to conduct the study "Nelfinavir in SLE: A pilot phase IIa clinical trial" by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the NIAMS (funding agency) and the Feinstein Institute for Medical Research (sponsor).

_____
Principal Investigator (Print)

_____
Principal Investigator Signature

_____
Date

IND 114834; Sponsor: Dr. Meggan Mackay, FIMR, NS-LIJHS

Title: Nelfinavir in Systemic Lupus Erythematosus: a pilot phase IIa clinical trial

1. INTRODUCTION

The overall goal of purpose of this exploratory Phase IIa clinical trial will be to investigate the immunomodulatory properties of nelfinavir, a protease inhibitor (PI) that is approved by the Food and Drug Administration (FDA) for treatment of Human Immunodeficiency Virus (HIV) disease, in Systemic Lupus Erythematosus (SLE). Specifically, we will determine the safety, tolerability and obtain a preliminary assessment of the efficacy of nelfinavir in patients with SLE that have mild to moderate disease activity and elevated titers of cross-reactive anti-dsDNA/anti-DWEYS peptide (anti-DNA/DWEYS) antibodies. The clinical trial is accompanied by mechanistic studies designed to investigate the *in vivo* effects of nelfinavir on anti-dsDNA antibody binding, interferon inducible genes (the IFN signature) and circulating cytokines in the in peripheral blood.

The hallmark of SLE is autoantibody production; anti-dsDNA antibodies in particular are highly specific for SLE. They have been eluted from kidney and brain tissue and are associated with disease severity and activity [1-2]. Deleterious effects of anti-dsDNA antibodies are mediated by direct binding to tissue substrate and formation of immune complexes that incite inflammatory responses through toll-like receptor (TLR) signaling, complement activation and Fc receptor binding. Anti-dsDNA antibodies are known to cross-react with protein epitopes, in particular with a DWEYS pentapeptide consensus sequence that appears in the N-Methyl D-Aspartate receptor (NMDAR) in brain and kidney. These cross-reactive anti-DNA/DWEYS antibodies contribute to lupus neuro- and nephrotoxicity and synthetic *d*-DWEYS peptide blocks pathogenic autoantibody binding *in vitro* and ameliorates kidney and brain complications in lupus models [3]. Certain PIs used for treatment of HIV disease may share a structural motif that is similar to that found in the DWEYS peptide. Preliminary *in vitro* ELISA studies in our lab have demonstrated that some of the PIs (nelfinavir, atazanavir, lopinavir, saquinavir, ritonavir, indinavir, and darunavir) can inhibit binding of a murine monoclonal anti-dsDNA antibody (R4A antibody) to DWEYS peptide, dsDNA and C1q (section 2.3). We have also demonstrated that one of the PIs, nelfinavir, inhibits binding of anti-dsDNA antibodies from lupus patients sera to dsDNA. These results have led us to hypothesize that one or more of the PIs may have beneficial effects in SLE through effects on anti-dsDNA antibody binding to antigen in addition to effects on pro-inflammatory cytokines and other inflammatory molecules such as high mobility group box protein 1 (HMGB-1). Current treatments of SLE include cytotoxic medications and treatment options that have a safer toxicity profile are urgently needed. PIs are currently used for treatment of HIV disease and are generally well-tolerated. Nelfinavir was chosen for use in this clinical trial because it has fewer potential side effects than the other PIs tested. We hypothesize that nelfinavir may have beneficial effects in the treatment of SLE through inhibition of anti-dsDNA antibody binding to target organs and, perhaps, through interfering with the formation of pro-inflammatory, DNA-containing immune complexes, pro-inflammatory cytokines and the IFN signature.

The planned clinical trial utilizes a Simon Two-Stage "optimal" trial design [4]. It will be conducted at the Feinstein Institute for Medical Research (FIMR) of the North Shore-LIJ Health System (NS-LIJ HS) and at least 7 other clinical sites. The clinical trial will be overseen by Drs. Meggan Mackay and Cynthia Aranow who co-direct the Clinical Research Unit in the Center for Autoimmune and Musculoskeletal Disease at the FIMR. Dr. Betty Diamond, head of the Center for Autoimmune and Musculoskeletal Disease, will also collaborate on this project and will be responsible for conducting the mechanistic studies.

The primary objective of this clinical trial is:

- To demonstrate that the protease inhibitor nelfinavir, administered orally to SLE subjects with mild to moderate disease activity, will decrease serum anti-dsDNA antibody binding by ≥35%.

Secondary, exploratory objectives are:

- To assess the safety and tolerability of nelfinavir in SLE patients.
- To assess the effect of nelfinavir on serum cytokine levels (IL-1, IL-6, and TNFα).
- To assess the effect of nelfinavir on serum levels of C3, C4 and CRP.
- To assess the effect of nelfinavir on the interferon signature.
- To assess the effect of nelfinavir on binding of serum titers of anticardiolipin antibodies.
- To demonstrate that nelfinavir does not increase lupus disease activity.
- To demonstrate that nelfinavir decreases disease activity.

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Disease Background

SLE is a chronic autoimmune disease characterized on a molecular level by pathogenic autoantibodies against nuclear antigens such as ds-DNA. Clinically, it is a disease characterized by recurrent flares that may involve any organ system and anti-dsDNA antibodies are associated with disease flares and severity, especially with active nephritis [5-7]. Anti-dsDNA antibodies are known to stimulate inflammatory responses through several mechanisms including immune complex formation with subsequent Fc receptor activation, TLR activation and complement activation. Additionally, direct binding of anti-dsDNA antibodies may modulate cell function or gene expression through Fc independent and dependent mechanisms. Pertinent to this clinical trial, a subset of anti-dsDNA antibodies that are cross-reactive with the DWEYS pentapeptide have been shown to bind to NMDA (N-methyl-d-aspartate) receptors found in neurons, leading to regional neuronal dysfunction and/or death and subsequent behavioral changes in mice [1, 8]. These same autoantibodies also cross react with glomerular antigens leading to tissue damage [9]. Inhibition of these parameters (tissue binding, immune complex formation, TLR stimulation) may lead to amelioration of the disease.

Many cells are involved in SLE pathogenesis; the principal players are thought to be B cells, T cells and dendritic cells. Monocytes are heterogenous circulating blood cells that make up approximately 10% of human peripheral blood leukocyte population. They rapidly mobilize to

sites of inflammation where inflammatory molecules initiate their differentiation into macrophages or dendritic cells [10]. The half life of a monocyte in circulation is approximately 72 hours [11]. This relatively short half life allows for a continuous repopulation of dendritic cells and macrophages. It may also allow for a rapid determination of potential immunomodulatory effects of certain drug therapies. Plasmacytoid dendritic cells (pDCs) are the main producers of interferon alpha (IFNα), an important cytokine involved in the pathogenesis of lupus [12-13]. IFNα stimulates dendritic cell maturation, which in turn promotes loss of tolerance and activation of autoreactive T and B lymphocytes, production of autoantibodies and immune complexes, and further production of IFNα.

High mobility group box protein 1 (HMGB1) is one of a group of highly conserved, ubiquitous, nuclear non-histone proteins, previously known as DNA-binding proteins, involved in the maintenance of nucleosome structure and regulation of gene expression. More recently, extracellular HMGB1 has been identified as a potent pro-inflammatory cytokine that is increased in serum and tissue during infection and inflammatory processes (reviewed in [14-15]). Large amounts of HMGB1 are released by a variety of tissue-specific cells as well as activated moncytes and macrophages in response to endotoxin or other inflammatory cytokines such as IL-1β, TNFα and IFNγ. HMGB1 released by apoptotic and necrotic cells also contributes to the extracellular pool. The pro-inflammatory effects of extracellular HMGB1 are mediated by cell surface receptors RAGE (Receptor for Advanced Glycation End Products), TLR 2, TLR4 and the intracellular TLR9 receptor. Engagement of any of these receptors leads to NF-κB activation via different intracellular signaling pathways thereby initiating and perpetuating the release of pro-inflammatory cytokines. There is also enhancement of DC maturation and resulting increased production of IFNα. High levels of extracellular HMGB1 have been associated with infection, particularly sepsis, and other diseases characterized by sterile inflammatory responses such as rheumatoid arthritis, Sjogrens and SLE [16-18]. Pertinent to our proposed study, serum HMGB1 levels are higher in SLE patients compared to healthy controls and levels correlate with disease activity and anti-dsDNA levels and inversely with serum C3 [19]. Molecules that bind to HMGB1 and prevent these proteins from binding to their targets may serve as potential therapeutics.

There are increasing data suggesting that, in addition to their anti-retroviral activity, PIs have immunomodulatory effects on macrophage, T cell and dendritic cell function [20-24]. PIs have been shown to inhibit TLR 2 and 4 activation resulting in decreased cytokine release from peripheral blood mononuclear cells in HIV patients and serum levels of inflammatory cytokines, such as TNFα and IL-6, are decreased in patients taking PIs [20]. Immunomodulatory effects of PIs have also been demonstrated in the murine model of experimental autoimmune encephalitis where administration of ritonivir decreased mononuclear cell infiltrate and inflammatory response [25]. Anti-retroviral drugs have been shown to prevent the sterile myocarditis induced by the intracellular accumulation of retroelement ssDNA in Trex-1 deficient mice; the animal model of human Aicardi-Goutières syndrome [26]. SLE is also associated with a genetic deficiency of Trex-1[27]. The ability of PIs to inhibit differentiation and maturation of DCs, accompanied by reduced secretion of inflammatory cytokines in response to TLR stimulation [21, 28], is particularly significant for SLE. IFNα, secreted by pDCs, has been linked to disease pathogenesis as well as disease activity [12-13]. These results have led us to hypothesize that one or more of the protease inhibitors may ameliorate the effects of SLE through its effects on

multiple cells involved in the aberrant inflammatory response associated with SLE. Additionally, based on results of studies done in our lab (section 2.3) we hypothesize that PIs may also alter anti-dsDNA antibody binding to its antigens (immune complexes, tissue antigens, C1q) or through an interaction with HMGB1, displacing DNA and/or preventing ligation with intra or extracellular receptors. In particular, prevention of HMGB1 binding to TLR 9 may decrease pDC maturation, differentiation and expression of IFNα.

2.2 Significance for Lupus treatment

The current management of patients with SLE is stratified by the degree of internal organ involvement; some therapeutic agents are used for mild to moderate disease with non-major organ involvement and others for severe disease associated with major organ involvement (renal and central nervous system). Non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials and glucocorticoids are generally used in the treatment of SLE without major organ involvement. Although these agents are widely used, there are only a few randomized controlled trials that demonstrate their efficacy in SLE. In addition, although studies show clinical improvement on these agents, it is clear that many patients continue to have residual disease activity (Tassiulas, I.O in Kelley's textbook of Rheum). Long term use of glucocorticoids contributes to significant toxicity such as continued immune suppression with increased risk of infection, osteoporosis, avascular necrosis, glaucoma, hypertension, hyperlipidemia, obesity and diabetes. Patients with moderate to severe and refractory disease are usually treated with more potent cytotoxic agents that suppress the immune system in a non-specific manner and have significant side effects. Cyclophosphamide, methotrexate and azathioprine, all synthetic antineoplastic drugs, and mycophenolate mofetil (MMF) are used to control disease activity and treat lupus manifestations with the potential of resulting in end organ failuret. Use of these agents is associated with multiple side effects including myelosuppression, infection, hemorrhagic cystitis, malignancy, and infertility (associated with use of cyclophosphamide).

Hydroxychloroquine is an antimalarial drug that, in addition to its antimicrobial properties, has also been recognized for its immunomodulatory effects [29-30]. It has been shown to be beneficial in the treatment of rheumatologic diseases such as SLE and rheumatoid arthritis. Proposed anti-inflammatory mechanisms of hydroxychloroquine include the disruption of lysosomal acidification with resultant inhibitory effects on cell signaling, protein production and secretion, eventually leading to a decrease in proinflammatory cytokine production (particularly IL-1, IL-6, TNFα, and IFN gamma) [29]. Hydroxychloroquine also has inhibitory effects on antigen receptor signaling in B and T lymphocytes, and antigen presentation. Most recently, hydroxychloroquine was found to inhibit activation of intracellular and cell surface TLRs [31-32]. Intracellular TLRs (in particular TLR 7, 8, and especially TLR 9) are important in as SLE as these receptors bind to host nucleic acids and nucleic acid containing immune complexes leading to enhanced production of IFNα with subsequent activation of B lymphocytes, T lymphocytes and dendritic cells. The effect of hydroxychloroquine on endosome acidification inhibits the binding of nucleic acids to intracellular TLRs. A similar mechanism of action may account for inhibitory properties of novel drug therapeutics such as PIs.

Management of active SLE frequently requires the use of multiple immunosuppressive and cytotoxic drugs. Almost all of these medications are unapproved and are used off-label; their use

has become "standard of care" by the rheumatologic community as they are often efficacious for the treatment of active disease. However, these immunosuppressive and cytotoxic medications are associated with multiple toxicities and their often have limited efficacy. Thus, therapies for SLE that are more selective and associated with a safer toxicity profile are urgently needed. We are therefore interested in testing drugs that have a known immunologic effect and that are known to be relatively safe in humans.

2.3 Summary of Pre-Clinical Studies

Previous studies have shown that a specific pentapeptide sequence, DWEYS, acts as a DNA mimetope and inhibits the binding of monoclonal anti-dsDNA antibodies, R4A (a murine monoclonal anti-dsDNA antibody) and G11 (a human monoclonal anti-dsDNA antibody) to DNA, DWEYS peptide and to mouse glomeruli by occupying the antigen-binding site of these antibodies [9]. The peptide sequence is also present in the NR2A and NR2B subunits of mouse and human NMDA receptors that are found on neurons throughout the brain and DWEYS peptide inhibits binding of the R4A antibody to neurons in the brain [1, 9]. The DWEYS peptide has also been shown to inhibit transfer of the IFN signature by sera from lupus patients *in vitro* to normal peripheral blood monocytes (PBMCs) (unpublished data). The IFN signature is comprised of a set of genes that are expressed following exposure to αIFN. The importance of αIFN in lupus pathogenesis has been well-established as lupus patients are found to have a pattern of increased expression of IFN-inducible genes [33].

The DWEYS peptide shares a structural motif with protease inhibitors and *in vitro* ELISA studies have demonstrated that some of the protease inhibitors, including nelfinavir, can inhibit binding of the R4A dsDNA antibody to the DWEYS peptide and DNA in a dose dependent manner (unpublished data)(Figure 1). The structural features of the DWEYS peptide were used to design a novel peptidomimetic molecule, FISLE-412, that has been shown to neutralize anti-dsDNA/DWEYS autoantibody binding to DNA both *in vitro* and *in vivo* in a murine lupus model [3]. The protease inhibitors inhibited binding of R4A to DNA and DWEYS peptide in a manner similar to that demonstrated by the peptidomimetic molecule, FISLE-412 (Figures 1 and 2a). Nelfinavir has also been shown to block renal deposition of the R4A antibody in the glomerular binding assay (unpublished data) (Figure 2b). Similarly, nelfinavir and other PIs block the neuronal apoptosis that occurs as a consequence of anti-dsDNA antibody binding to NMDAR on neurons in the brain (unpublished data) (Figure 2c). Measurement of anti-dsDNA binding in sera from four lupus patients with active disease and elevated titers of anti-dsDNA antibodies was decreased after pre-incubation with nelfinavir *in vitro* (unpublished data)(Figure 3). These data support our hypothesis that nelfinavir may alter anti-dsDNA antibody binding *in vivo*, thereby preventing the pro-inflammatory consequences of anti-dsDNA antibody binding. Additional potential anti-inflammatory effects of nelfinavir are the decreased cytokine expression in stimulated PBMC (Figure 4). While the peptidomimetic molecule, FISLE-412, is undergoing development as a potential therapeutic agent, we anticipate that this clinical trial will demonstrate the biologic efficacy in vivo of nelfinavir, a protease inhibitor acting as a decoy antigen for anti-dsDNA antibodies in SLE. The re-purposing of an FDA-approved medication that has a strong safety profile for an alternate use will allow for rapid transition to the clinic for a disease in great need of novel therapeutic strategies.

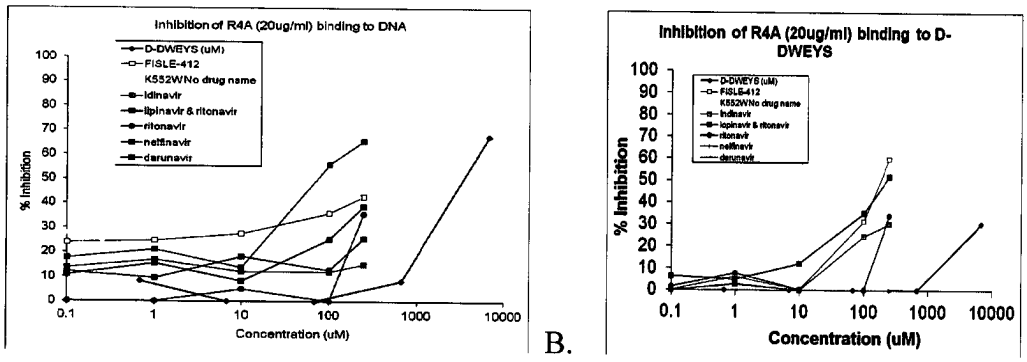


Figure 1. Inhibition of murine monoclonal anti-dsDNA antibody, R4A, binding by protease inhibitors. ELISA assays were performed to test binding of the monoclonal R4A antibody to DNA and the DWEYS peptide with and without protease inhibitors at concentrations of 1, 10, 100, 1000 and 10000 uM. **A.** % inhibition of R4A binding to DNA **B.** % inhibition of R4A binding to the DWEYS peptide. FISLE-412 is a peptide mimetope of DWEYS that is known to effectively inhibit R4A binding to DNA or the DWEYS peptide. K552W is saquinivir.

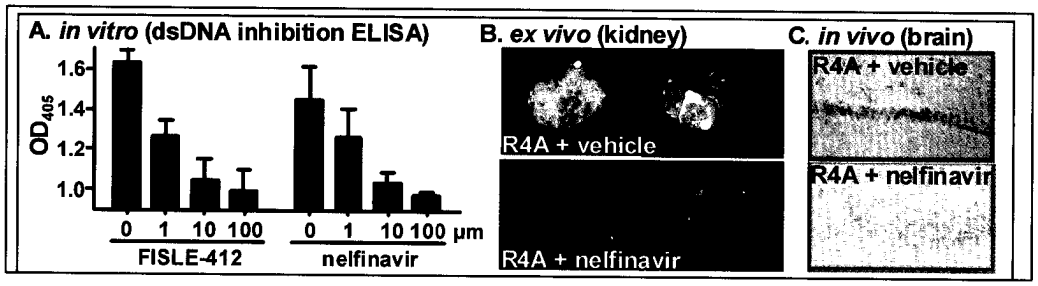


Figure 2. Nelfinavir inhibits pathologic anti-DNA antibodies *in vivo, ex vivo* (kidney) and *in vivo* (brain). A) Like peptidomimetic FISLE-412, nelfinavir inhibits human SLE autontibodies from binding to dsDNA in a dose-dependent manner. B) Pre-incubation with nelfinavir (dim stain, bottom) suppresses pathogenic R4A antibody deposition in glomeruli relative to vehicle-treated R4A (bright stain, top). C) Nelfinavir blocks neurotoxicity of R4A antibodies *in vivo*. Panels show the region around the CA-1 hippocampal injection site of R4A pre-incubated with vehicle (top) or nelfinavir (bottom); neurotoxicity is indicated by TUNEL positive (brown) staining.

Figure 3. Inhibition of lupus patient sera binding to DNA by nelfinavir. Sera collected from four lupus subjects (F008, F078, F107, F156) with moderately active disease (defined as having a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) ≥4) and elevated anti-dsDNA antibody titers was used in an ELISA assay for binding to DNA. The addition of nelfinavir in micromolar concentrations of 1, 10 and 100 resulted in decreased DNA binding by 59%, 60% and 56% respectively. Increasing concentrations of nelfinavir did not alter the percent inhibition of DNA binding.

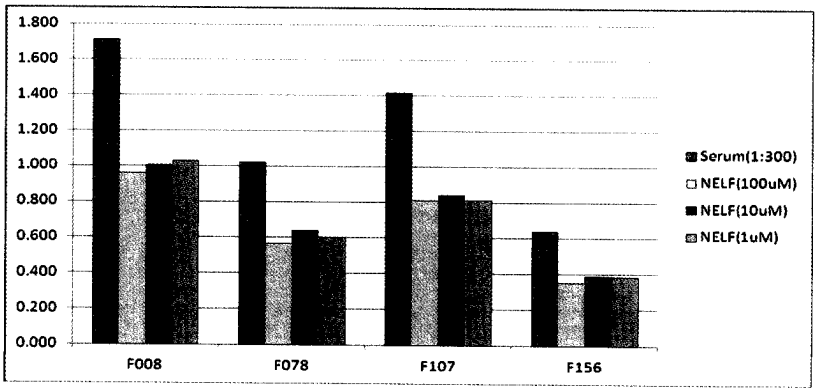
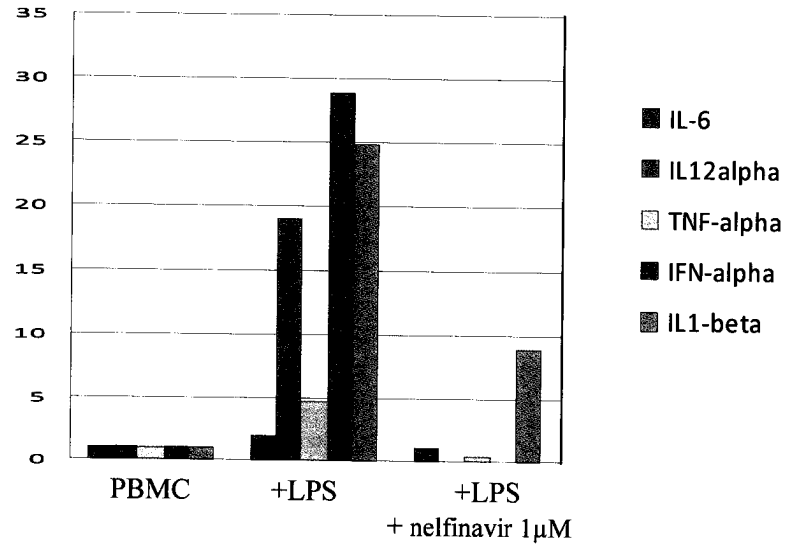


Figure 4. Cytokine response
Addition of nelfinavir to PBMC stimulated with lipopolysacharide (LPS) results in decreased expression of pro-inflammatory cytokines IL-6, IL-12α, TNF α, IFN α and IL-1β.



3. STUDY DRUG INFORMATION

3.1 Rationale for use of study drug (nelfinavir)

As demonstrated in Figure 1, several of the PIs inhibit anti-dsDNA antibody binding to DNA and DWEYS peptide. Our decision to use nelfinavir for this clinical trial was based on an extensive review of potential drug toxicities. Nelfinavir was specifically chosen for its relatively safe profile in comparison to the other PIs and we hypothesize that nelfinavir will be well tolerated in stable SLE patients. We have employed an open-label trial with no placebo arm for the following primary reasons: (i) nelfinavir is safe and well-tolerated in HIV patients, (ii) after excluding subjects taking contraindicated medications, we have no reason to think that those enrolled will be at increased risk for toxicity to nelfinavir, (iii) we are dosing at or below the recommended dose of nelfinavir in HIV patients, (iv) we have carefully pre-determined stopping rules for toxicity, and (v) as an added immediate safety precaution, we will enroll the first four subjects sequentially with a 2 wk observation delay prior to enrolling the next subject.

3.2 Drug Description

Nelfinavir, the brand name is Viracept, is an inhibitor of the human immunodeficiency virus (HIV) protease. It is currently licensed as an antiviral medication, in conjunction with other protease inhibitors, for the treatment of HIV infection. Protease inhibition prevents the cleaving of the *gag* and *gag-pol* polyprotein and this in turn leads to the production of non-infectious viruses. Nelfinavir is [3S[2(2S*, 3S*), 3α,4aβ,8aγ]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide monomethanesulfonate and has a molecular weight of 663.90 (567.79 as the free base). Nelfinavir is a white amorphous powder, slightly soluble in water at pH < 4 and is freely

soluble in methanol, ethanol, 2-propanol and propylene glycol. Tablets are available for oral administration as a light blue, capsule-shaped tablet with a clear film coating in 250 mg strength (as nelfinavir free base) and as a white oval tablet with a clear film coating in 625 mg strength (as nelfinavir free base). Each tablet contains the following common inactive ingredients: calcium silicate, crospovidone, magnesium stearate, hypromellose, and triacetin. The 250 mg tablet contains FD&C blue #2 powder and the 625 mg tablet contains colloidal silicon dioxide. Nelfinavir oral powder is available for oral administration in a 50 mg/g strength (as nelfinavir free base) in bottles. The oral powder contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor. Nelfinavir has a plasma half life of approximately 3.5 to 5 hours and a steady state of the drug is achieved in 6 days [34-35]. It is metabolized by several cytochrome P-450 enzymes including CYP3A4, CYP2C19, CYP2C9, and CYP2D6. The recommended nelfinavir dose for treating adults with HIV or AIDS is 1250 mg (either five 250 mg tablets or two 625 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily (Viracept Prescribing Information. Agouron Pharmaceuticals Inc, 2008). The research pharmacy at North Shore/LIJ Health System will obtain approved drug, nelfinavir/viracept, from Alexion Pharmaceuticals (352 Knotter Drive, Cheshire, CT 06410) through their specialty pharmaceutical distributor, Cardinal Health (7000 Cardinal Place, Dublin, Ohio 43017) The research pharmacy at North Shore/LIJ Health System will act as the central pharmacy for all sites in the study. As such, the central pharmacy will store the study drug and dispense drug to all participating sites as needed. Once a subject has been screened for the study, the site coordinator will contact the central study coordinator at the FIMR and an adequate amount of drug for that subject to complete the study will be shipped overnight from the central pharmacy to that site so that enrollment is not delayed. Unused or expired drug will be destroyed either at the local participating site or in the central pharmacy. Details for drug storage, maintenance and disposal specifications can be found in the Manual of Procedures.

4. KNOWN AND POTENTIAL RISKS and BENEFITS

4.1 Risks

Nelfinavir is FDA approved for use as an anti-retroviral agent in patients with HIV disease. Though generally well-tolerated in the HIV population, nelfinavir has potential risks associated with its use. The most frequent adverse events are gastrointestinal complaints, most commonly diarrhea, which may be controlled with antidiarrheal agents such as loperamide. In two large clinical trials that included 606 patients, diarrhea occurred in 14%-32% [36]. Other side effects include abdominal pain, nausea, vomiting, rash, leucopenia, anemia, thrombocytopenia occurring with a frequency of 1% to 10%. If a subject is experiencing mild gastrointestinal toxicity attributed to nelfinavir, the dose for that subject may be decreased to 750 mg orally twice daily after discussion with the participating site PI. Lipodystrophy, or abnormal body fat deposition, is another adverse effect that has been reported after prolonged use of all protease inhibitors; duration of therapy ranged from 4 weeks to 18 months. Fat deposition occurs in the neck and shoulders or midsection. It can occur in association with dyslipidemia, alluding to an abnormality in lipid metabolism. Protease inhibitors may also lead to hyperglycemia or exacerbate pre-existing diabetes mellitus. This adverse effect however is noted to be infrequent, occurring in <1% of patients (medscape reference online: http://reference.medscape.com/drug/viracept-nelfinavir-342622#0.)

As of August 17, 2015, there have been two reports in two separate subjects enrolled in this clinical trial of nelfinavir in SLE subjects of a serum sickness type of reaction occurring approximately 10 days after starting nelfinavir. The reaction was characterized by the simultaneous onset of raised, erythematous tender nodules on both hands, increased erythematous inflammatory rash on the face, chest and/or arms and new or worsening poyarthritis. All of the symptoms resolved within 2-3 days after stopping the nelfinavir.

Nelfinavir is classified as an FDA Pregnancy Category B drug; there is no evidence of human risk in controlled studies. Nelfinavir crosses the placenta and no increased risk of overall birth defects following first trimester exposure in humans has been reported to the antiretroviral pregnancy registry. Nelfinavir is recommended for use in HIV positive women for prophylaxis of perinatal transmission if alternative regimens are not tolerated. Because of drug metabolism via the cytochrome p-450 enzymes, there are multiple potential interactions between Nelfinavir and other drugs. More specifically, nelfinavir inhibits cytochrome P450 3A (CYP3A) and therefore may affect serum levels of the following: benzodiazepines, anti-arrhythmics, calcium channel blockers, oral contraceptives, statins, among others (major interactions are listed in Table 1). To reduce potential toxicity, we plan to exclude subjects that are taking medications metabolized by the cytochrome P450 system and that have major interactions with nelfinavir. In addition, there are no known interactions between the immunosuppressive medications commonly used for treatment of SLE, hydroxychloroquine, corticosteroids, azathioprine, MMF, methotrexate, cyclophosphamide, and nelfinavir. There are no reasons to think lupus subjects would be more susceptible to toxicities associated with nelfinavir than individuals with HIV disease. Due to the frequency of reports of hyperglycemia attributed to nelfinavir in the post-marketing period, all subjects will be counseled to look for symptoms of hyperglycemia (increased thirst, increased hunger, frequent urination and weight loss). They will be asked about these symptoms at all of the study visits following dosing with the study drug and serum glucose will be measured on Days 14, 28, 56 and 84 so it is unlikely that nelfinavir-induced hyperglycemia would be missed.

Table 1: Major interaction between Nelfinavir and drug classes with likely adverse effect

Drug Class	**Example of Drug**	**Possible adverse event**
Antiarrythmics	Amiodarone, Quinidine	Cardiac arrhythmias
Sedative/Hypnotic	Midazolam, Triazolam	Prolonged sedation/respirator depression
Ergot Derivative	Ergotamine, Dihydroergotamine, methylergonovine	Ergot toxicity: extremity vasospasm/ischemia
Neuroleptic	Pimozide	Cardiac arrhymias
Proton Pump Inhibitor	Omeprazole	Decreased level/effect of nelfinavir
HMG-CoA reductase inhibitors	Lovastatin, Simvastatin	Risk of Myopathy/Rhabdomyolysis
Antimicrobial	Rifampin	Decreased drug effect
Herbal Product	St. John's wort	Decreased Drug effect

Alpha 1-adrenoreceptor antagonist	Aluzosin	Increased drug effect: hypotension
GI Motility Agent	Cisapride	Cardiac arrhythmias
PDE5 Inhibitors	Sildenafil (Revatio)	Visual disturbances, hypotension, prolonged erection, and syncope

Adapted from Package Insert 4/2012

4.2 Benefits

We anticipate that, based on their reported immunomodulatory effects and the preliminary data from our lab on anti-dsDNA antibody binding, nelfinavir may modulate inflammatory responses in SLE thereby decreasing disease activity.

5. METHODS

5.1 Design

This clinical trial is designed to assess the effect of nelfinavir on dsDNA binding in SLE patients with mild to moderate disease activity defined as follows:

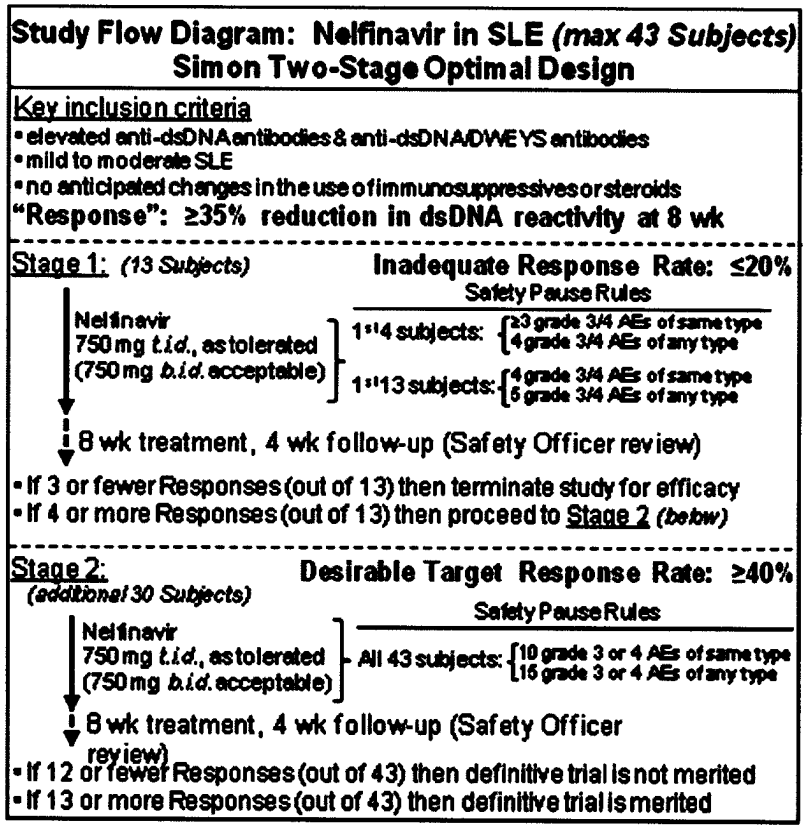
- a minimum SELENA SLEDAI score of 2 (excluding points for anti-dsDNA antibodies and complement)
- no renal or nervous system disease activity
- no BILAG A criteria
- no expectation by the investigator that corticosteroids will need to be added or doses increased during the trial period
- no expectation by the investigator that immunosuppressive medication will need to be added or doses increased during the trial period

The Simon Two-Stage trial design limits exposure to study drug that is not effective and we believe that this trial design provides an efficient method for assessment of an FDA approved medication for HIV disease for another purpose. This study design does not have a placebo arm; all subjects will be dosed with nelfinavir 750 mg orally thrice daily. If the thrice daily dose is not tolerated, subjects will be allowed to decrease the dose to twice daily. For both stages of the trial the dosing period is 8 weeks followed by a 4 week observation period. A maximum of 13 subjects will be enrolled in the first stage of the trial followed by a maximum enrollment of an additional 30 in the second stage. The primary endpoint or "Response" is defined as a $\geq$35% reduction in serum anti-dsDNA antibody titer from baseline values to end of treatment (8 weeks). This definition is based on established changes in anti-dsDNA titers in other lupus trials. We will test the null hypothesis that the true objective Response rate is $\leq$20% (Inadequate Response Rate, which would not be clinically meaningful) versus the alternative hypothesis that the true Response rate is $\geq$40% (Desirable Target Response Rate, Figure 5). Importantly, these Response Rates are consistent with results from other lupus clinical trials (e.g., immunosuppressives, steroids) where $\leq$20% was considered not significant and $\geq$40% was clinically meaningful. With a significance level of 0.05 and a power of 0.80, a maximum of 43 evaluable subjects (13 in Stage 1 plus 30 in Stage 2) will be required to assess the objective Response rate (Figure 5) [4]. From among the 13 subjects enrolled in Stage 1; if 3 or fewer objective Responses are observed, then the trial will be terminated (Figure 5A). If 4 or more objective Responses are observed in the first 13 subjects, however, the study will be expanded to enroll an additional 30 patients (Stage 2; Figure 5B). At the end of the study, if 13 or more Responses are observed, then the null hypothesis that the true response probability is $\leq$20% will

be rejected and further investigation of nelfinavir in this patient population is warranted (Figure 5B) [4].

Treatment will be 750 mg nelfinavir thrice daily dosing (*t.i.d.*), if a given subject cannot tolerate this dose (*e.g.*, due to nausea), we will allow a step down to twice daily dosing (*b.i.d.*). Subjects and/or their insurance companies will not be charged for the nelfinavir; the study medication will be provided to all subjects free of charge. Compliance will be monitored by pill count – all evaluable subjects must maintain ≥80% compliant (*i.e.*, ≥135 of 168 pills). While study endpoints will be determined immediately following treatment (8wk), durability will be assessed after a 4 week follow-up period. Because a Simon Two-Stage trial contains no placebo arm, we will be especially vigilant regarding safety. The Safety Officer and NIAMS have ultimate authority to address safety but we have incorporated clear stopping rules into the trial design (see section 5.4.2 for details).

Figure 5. Study Design Flow Diagram
Simon Two-Stage: Nelfinavir in SLE (max 43 subjects)



5.2 Subject Selection

Written informed consent must be obtained prior to the subject undergoing any study-related procedure, including screening tests. All subjects will be required to fulfill the entry criteria listed below

Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment into the study:

1. Subject is capable of providing written informed consent
2. Subject is ≥ 18 years old and ≤ 65 years old
3. Meets at least 4 of 11 modified American College of Rheumatology (ACR) (1997) Revised Criteria for the Classification of Systemic Lupus Erythematosus

4. Has mild to moderate disease activity defined as
   - A minimum SLEDAI score of 2 excluding points for serology (anti-dsDNA antibody and complement)
   - No active renal or nervous system disease
   - No BILAG A in any organ system
   - No expectation by the investigator that corticosteroids will need to be added or doses increased during the 8 week treatment period for any reason
   - No expectation by the investigator that immunosuppressive medication will need to be added or doses increased during the 8 week treatment period
5. Has elevated titers of anti-ds DNA antibody at the time of screening (defined as the titer that meets criteria for "high" in the Core Laboratory at the North Shore/LIJ Health Systems; unequivocal high titer as opposed to borderline, indeterminate or intermediate).
6. Has elevated titers of cross-reactive anti-DNA/DWEYS antibodies at the time of screening (the assays for anti-DNA/DWEYS antibodies will be performed in Dr. B. Diamond's laboratory; study sites will be notified of results within 3 days of receipt of the samples).
7. If on glucocorticords, the dose must be ≤ 10mg daily and stable or decreasing 4 weeks prior to baseline
8. If on immunosuppressive or immunomodulatory medication such as azathioprine, methotrexate, leflunomide, mycophenolate, belimumab or hydroxychloroquine, the dose must have been stable for the 3 months prior to screening, and expected to remain stable over the course of the study.
9. Males and females with potential for reproduction must agree to practice effective birth control measures (2 approved methods of contraception). Nelfinavir can decrease serum levels of oral contraceptives; the slightly increased risk of pregnancy due to an interaction between oral contraception and nelfinavir will be discussed when appropriate and the requirement for a second approved method of contraception will be addressed.

Exclusion Criteria

Subjects who meet any of the following criteria are disqualified from enrollment in the study:

1. Current or prior treatment with rituximab or anti-CD22 monoclonal antibody in the 12 months prior to this study or any other biologic agent for 90 days prior to this study
2. Treatment with cyclophosphamide within the 6 months prior to screening
3. Increase in glucocorticoid dose within 4 weeks of screening or addition of a DMARD in the three months prior to study
4. A history of drug or alcohol abuse within the 6 months prior to screening
5. Elevated LFT's:
    - ALT or AST $\geq$ 2 x upper limit of normal at screening
    - serum unconjugated bilirubin > 3mg/dL at screening
6. Dialysis or serum creatinine >1.5mg/dL
7. Hypercholesterolemia: total cholesterol >230 mg/dL or LDL >150 mg/dl or hypertriglyceridemia (triglyceride >200mg/dL) at screening
8. Laboratory/clinical evidence of: pancreatitis: amylase/lipase >3x upper limit of normal at screening
9. Known current/active infections including HIV, Hepatitis B, Hepatitis C
10. History of cancer, excluding skin cancers (squamous cell or basal cell that have been treated)
11. Known active tuberculosis or untreated tuberculosis
12. Hemoglobin < 8 g/dL
13. Expectation by the investigator to increase corticosteroid or immunosuppressive, or immunomodulatory medication dose at screening, baseline, or over the course of the study
14. Pregnancy or lactation
15. Consumption of > 2 cups of grapefruit juice per day
16. Treatment with medications metabolized using the cytochrome P3A4 pathway, such as cyclosporine, tacrolimus, gemfibrozil, niacin, itraconazole, ketoconazole, erythromycin, azithromycin, clarithromycin, bosentan, nefazodone, tricyclic antidepressants
17. Treatment with any drugs known to interact with nelfinavir that include amiodarone, quinidine, midazolam, triazolam, ergotamine, dihydroergotamine, methylergonovine, pimozide, lovastatin, simvastatin, rifampin, St. John's Wort, aluzosin, cisapride and sildenafil.
18. Any condition that, in the opinion of the Investigator, would jeopardize the subject's safety following exposure to the study drug.

5.3 Concomitant medications

Use of corticosteroids, immunosuppressive or immunomodulatory medications are allowed per inclusion and exclusion criteria. Doses of these agents must remain stable throughout the study period. NSAIDS and Tylenol are allowed but should be held overnight or for 12 hours prior to each assessment of disease activity on Days 1, 28, 56 and 84. Subjects will be asked not to start new over the counter medications, nutritional supplements or vitamins during the course of the study.

Use of increased or added doses of corticosteroids for purposes other than SLE treatment are discouraged, however, in the event of medical necessity can be allowed in the following circumstances:

- Daily doses up to a maximum of 30 mg per day will be allowed for a maximum of 2 days if the last dose is taken more than 5 days from the day 56 assessment.

5.4 Study Procedures
(Note: see **MOOP Figure 1** for a Schedule of Events that lists all study procedures)

All study information will be collected on Case Report Forms (CRFs) that will be scanned and emailed to the Central Study Coordinator (CSC) at the FIMR within 7 days of each study visit. For sites that do not have secure encrypted email, the CRFs will be transmitted via a secure fax to the CSC at the FIMR. A dedicated data transfer technician will be responsible for transferring data from the CRFs to the secure database in the Biostatistics Unit at the FIMR.

5.4.1 Study Visits
Screening Visit: Each potential participant will provide written informed consent and no study procedures will be done prior to this. Consenting subjects will participate in a screening visit where assessments will be performed to establish eligibility. The screening visit will include assessments of the following:

- Demographic data
- Medical history, including American College of Rheumatology criteria for SLE
- Physical exam
- Medication review
- Tuberculosis exposure*
- Laboratory assessments:
    - **Central Laboratory:** Serum to be sent overnight to the Coordinating Center at the FIMR. The CSC will be responsible for sending de-identified samples to the *Diamond Laboratory at the FIMR* for anti-DNA/DWEYS antibody testing and to the *Core Laboratory in the North Shore LIJ Health System* for anti-dsDNA antibodu testing. Results will be available to the participating sites within 3 days of receipt at the FIMR. See **MOOP Appendix E** for processing, storing and shipping details.
    - **Local Laboratory** (at the participating site):
        - CBC with differential
        - Comprehensive chemistry
        - C3, C4
        - Urinalysis with micro
        - HIV, Hepatitis B, Hepatitis C
        - Serum βHCG for women of childbearing potential
        - Subjects will be asked to return for a fasting lipid profile
- Disease activity assessments:
    - SELENA SLEDAI
    - BILAG

*All subjects will be tested for latent infection with mycobacterium tuberculosis using the purified protein derivative (PPD) skin test or the Quantiferon Gold test unless 1) they have a history of a positive PPD and have undergone treatment or 2) they have documentation of a negative TB test (PPD or Quantiferon Gold) within the preceding 3 months from screening. PPD will be administered subcutaneously and subjects will be asked to return for the PPD reading in 48-72 hours as per PPD guidelines. If preferred, the Quantiferon Gold test can be sent instead of the PPD. All subjects with a positive PPD or Quantiferon Gold test that have not previously received a full course of treatment are excluded from this study (see exclusion criteria). If a subject has received the BCG vaccine and the PPD test is equivocal, the investigator may choose to use the quantiferon gold test. Subjects with positive PPD or quantiferon gold tests who have not previously been treated for TB will be referred for further evaluation (e.g. including chest X-ray and sputum culture and smear).

Day 1 (initiation of treatment):
NSAIDS and Tylenol should be held overnight or for 12 hours prior to the assessments on Day 1. The following assessments will take place on Day 1 prior to dosing with the study medication for those subjects who meet eligibility criteria ***and are returning for the Day 1 visit more than 10 days after the screening visit***:

- Medical history
- Adverse event review
- Physical exam
- Medication review
- For women of childbearing potential a urine pregnancy test must be negative prior to dosing with study medication
- Laboratory assessments prior to dosing with study medication
    - **Local Laboratory** (at the participating site)
        - CBC with differential
        - Comprehensive chemistry, amylase, lipase
        - C3, C4
        - Urinalysis with micro
    - **Central Laboratory** (see **MOOP Appendix E** for processing, storage and shipping instructions)
        - anti-dsDNA and anti-DNA/DWEYS antibody titers,
        - antibodies to Sm, RNP, Ro, La, anticardiolipin antibodies: IgG, IgA, IgM
        - cytokine levels
        - interferon signature
        - CRP
- Disease activity assessments:
    - SELENA SLEDAI
    - BILAG
    - Joint count
    - PGA
    - SLICC Damage Index
- Patient Assessments:
    - LupusPRO
    - Patient global assessment (PtGA)

- Dispense 30 days of study drug, nelfinavir

For subjects that meet eligibility criteria returning for the Day 1 visit ***within 10 days of the screening visit,*** the SELENA SLEDAI assessment obtained at screening should be used as the Day 1 SELENA SLEDAI and a repeat CBC, comprehensive chemistry, C3, C4 and urinalysis with micro will not be performed. The following assessments will be performed for these subjects at the Day 1 visit prior to dosing with the study medication:

- Medical history
- Adverse event review
- Physical exam
- Medication review
- For women of childbearing potential a urine pregnancy test must be negative prior to dosing with study medication
- Disease activity assessments:
    - BILAG
    - Joint count
    - PGA
    - SLICC Damage Index

- Patient Assessments:
    - LupusPRO
    - Patient global assessment (PtGA)
- Laboratory assessments prior to dosing with study medication
    - **Central Laboratory** (see MOOP Appendix E for processing, storage and shipping instructions)
        - anti-dsDNA and anti-DNA/DWEYS antibody titers,
        - antibodies to Sm, RNP, Ro, La, anticardiolipin antibodies: IgG, IgA, IgM
        - cytokine levels
        - interferon signature
        - CRP
- Dispense 30 days of study drug, nelfinavir

Day 7: All subjects will return on Day 7 for the following assessments:

- Medical history, including assessment of nelfinavir tolerability
- Adverse event review
- Physical exam
- Medication review (including a pill count for study drug; nelfinavir)
- Hyperglycemia assessment: Subjects will be asked about symptoms of hyperglycemia: increased thirst, increased hunger, frequent urination and weight loss. If symptoms are present, a serum glucose (using a fingerstick measurement or a chem-7 measurement) should be obtained. Based on the serum glucose level, the following guidelines should be followed:
    - Grade 1 or 2 Hyperglycemia (serum glucose < 250)
        - In subjects with pre-existing diabetes: these subjects can be allowed to continue in the study with intensification of their diabetes regimen and glucose monitoring

        - In subjects with no history of hyperglycemia or diagnosis of diabetes: these subjects should be taken off the study medication and discontinued from the study (section 6.1.1).
    - Grade 3 hyperglycemia (serum glucose > 250): subjects should be taken off study medication, discontinued from the study (section 6.1.1), treated and followed for resolution of the hyperglycemia.

Day 14: Subjects will be asked to fast after midnight the night prior to this visit. All subjects will return on Day 14 for the following assessments:

- Medical history, including assessment of nelfinavir tolerability
- Adverse event review
- Physical exam
- Medication review (including a pill count for study drug; nelfinavir)
- Hyperglycemia assessment: Subjects will be asked about symptoms of hyperglycemia: increased thirst, increased hunger, frequent urination and weight loss. If symptoms are present, a serum glucose (using a fingerstick measurement or a chem-7 measurement) should be obtained. Based on the serum glucose level, the following guidelines should be followed:
    - Grade 1 or 2 Hyperglycemia (serum glucose < 250)
        - In subjects with pre-existing diabetes: these subjects can be allowed to continue in the study with intensification of their diabetes regimen and glucose monitoring
        - In subjects with no history of hyperglycemia or diagnosis of diabetes: these subjects should be taken off the study medication and discontinued from the study (section 6.1.1).
    - Grade 3 hyperglycemia (serum glucose > 250): subjects should be taken off study medication, discontinued from the study (section 6.1.1), treated and followed for resolution of the hyperglycemia.
- Laboratory assessments
    - **Local Laboratory** (at the participating site)
        - CBC with differential
        - Comprehensive chemistry, amylase, lipase
        - Urinalysis with micro
        - Fasting lipid profile
    - **Central Laboratory** (see **MOOP Appendix E** for processing, storage and shipping instructions)
        - anti-dsDNA and anti-DNA/DWEYS antibody titers,
        - antibodies to Sm, RNP, Ro, La, anticardiolipin antibodies: IgG, IgA, IgM
        - cytokine levels
        - interferon signature
        - CRP

Day 28: Subjects will be asked to refrain from taking Tylenol or NSAIDS and to fast after midnight the night prior to this visit. All subjects will return on Day 28 for the following assessments:

- Medical history, including assessment of nelfinavir tolerability
- Adverse event review
- Physical exam
- Medication review (including a pill count for study drug; nelfinavir)
- For women of childbearing potential a urine pregnancy test must be negative prior to continued dosing with study medication
- Hyperglycemia assessment: Subjects will be asked about symptoms of hyperglycemia: increased thirst, increased hunger, frequent urination and weight loss. If symptoms are present, a serum glucose (using a fingerstick measurement or a chem-7 measurement) should be obtained. Based on the serum glucose level, the following guidelines should be followed:
    - Grade 1 or 2 Hyperglycemia (serum glucose < 250)
        - In subjects with pre-existing diabetes: these subjects can be allowed to continue in the study with intensification of their diabetes regimen and glucose monitoring
        - In subjects with no history of hyperglycemia or diagnosis of diabetes: these subjects should be taken off the study medication and discontinued from the study (section 6.1.1).
    - Grade 3 hyperglycemia (serum glucose > 250): subjects should be taken off study medication, discontinued from the study (section 6.1.1), treated and followed for resolution of the hyperglycemia.
- Disease activity assessments:
    - SELENA SLEDAI
    - BILAG
    - Joint count
    - PGA
- Patient Assessments:
    - LupusPRO
    - Patient global assessment (PtGA)
    - **Local Laboratory** (at the participating site)
        - CBC with differential
        - Comprehensive chemistry, amylase, lipase
        - C3, C4
        - Fasting lipid profile
        - Urinalysis with micro
    - **Central Laboratory** (see **MOOP Appendix E** for processing, storage and shipping instructions)
        - anti-dsDNA and anti-DNA/DWEYS antibody titers,
        - antibodies to Sm, RNP, Ro, La, anticardiolipin antibodies: IgG, IgA, IgM
        - cytokine levels
        - interferon signature
        - CRP
- Dispense 30 days of study drug, nelfinavir

Day 56 (last day of study drug): Subjects will be asked to refrain from taking Tylenol or NSAIDS and to fast after midnight the night prior to this visit. Subjects will return on Day 56 for the following assessments:

- Medical history, including assessment of nelfinavir tolerability
- Adverse event review
- Physical exam
- Medication review (including a pill count for study drug; nelfinavir)
- For women of childbearing potential a urine pregnancy test will be done
- Hyperglycemia assessment: Subjects will be asked about symptoms of hyperglycemia: increased thirst, increased hunger, frequent urination and weight loss. If symptoms are present, a serum glucose (using a fingerstick measurement or a chem-7 measurement) should be obtained. Based on the serum glucose level, the following guidelines should be followed:
    - Grade 1 or 2 Hyperglycemia (serum glucose < 250)
        - In subjects with pre-existing diabetes: these subjects can be allowed to continue in the study with intensification of their diabetes regimen and glucose monitoring
        - In subjects with no history of hyperglycemia or diagnosis of diabetes: these subjects should be taken off the study medication and discontinued from the study (section 6.1.1).
    - Grade 3 hyperglycemia (serum glucose > 250): subjects should be taken off study medication, discontinued from the study (section 6.1.1), treated and followed for resolution of the hyperglycemia.
- Disease activity assessments:
    - SELENA SLEDAI
    - BILAG
    - Joint count
    - PGA
- Patient Assessments:
    - LupusPRO
    - Patient global assessment (PtGA)
    - **Local Laboratory** (at the participating site)
        - CBC with differential
        - Comprehensive chemistry, amylase, lipase
        - C3, C4
        - Fasting lipid profile
        - Urinalysis with micro
    - **Central Laboratory** (see **MOOP Appendix E** for processing, storage and shipping instructions)
        - anti-dsDNA and anti-DNA/DWEYS antibody titers,
        - antibodies to Sm, RNP, Ro, La, anticardiolipin antibodies: IgG, IgA, IgM
        - cytokine levels
        - interferon signature

- CRP

Day 84 (end of study): Subjects will be asked to refrain from taking Tylenol or NSAIDS after midnight the night prior to this visit. Subjects will return on Day 84 for the following assessments:

- Medical history
- Adverse event review
- Physical exam
- Hyperglycemia assessment: Subjects will be asked about symptoms of hyperglycemia: increased thirst, increased hunger, frequent urination and weight loss.
- Disease activity assessments:
  - SELENA SLEDAI
  - BILAG
  - Joint count
  - PGA
- Patient Assessments:
  - LupusPRO
  - Patient global assessment (PtGA)
- Laboratory assessments prior to dosing with study medication
  - **Local Laboratory** (at the participating site)
    - CBC with differential
    - Comprehensive chemistry, amylase, lipase
    - C3, C4
    - Urinalysis with micro
  - **Central Laboratory** (see **MOOP Appendix E** for processing, storage and shipping instructions)
    - anti-dsDNA and anti-DNA/DWEYS antibody titers,
    - antibodies to Sm, RNP, Ro, La, anticardiolipin antibodies: IgG, IgA, IgM
    - cytokine levels
    - interferon signature
    - CRP

Unscheduled visits: At screening all subjects will be given investigator contact information for 24 hour use in the event of an emergency. At each study visit, all subjects will be reminded to call study personnel and arrange for an "unscheduled" visit immediately if they feel ill in any way or experience or have concerns about their health. Subjects will be evaluated and appropriate interventions will be put into place at the discretion of the investigator. If there has been a change in disease activity and an unscheduled visit occurs more than 10 days after an evaluation for disease activity using the SELENA SLEDAI, an assessment of disease activity using the SELENA SLEDAI should be done including the appropriate tests required to complete the SELENA SLEDAI.

Visit Windows: The visits on Days 7 and 14 allow a one day window on either side. The visits on Days 28, 56 and 84 allow for a 3 day window on either side.

5.4.2 Endpoints:

1. Primary endpoint

The primary endpoint is a mechanistic endpoint: inhibition of anti-dsDNA binding. Inhibition of anti-dsDNA binding will be determined by assessment of: change in anti-ds DNA antibody titers from baseline to Day 56.
Blood obtained for the anti-dsDNA antibody titers on Day 1 before administration of nelfinavir and on Days 14, 28, 56 and 84 will be spun and the serum stored at -20 or -80 degrees at each site. Following completion of Day 56, all of the Central Laboratory samples obtained thus far for each subject (Days 1-56 inclusive) will be batched and sent to the central site at the FIMR. Serum samples for anti-dsDNA antibodies from individual subjects on Days 1, 14, 28 and 56 will then be run simultaneously in the Core Laboratory in the North Shore/LIJ Health System using an enzyme immunoassay. This will allow for an ongoing statistical analysis of response so that the rules of the Simon Two Stage design can be applied. Mechanistic blood samples collected on Day 84 can all be frozen as individual subjects complete the study and all of these samples can then be batched at the participating sites and sent to the Coordinating Center at the FIMR at study completion.

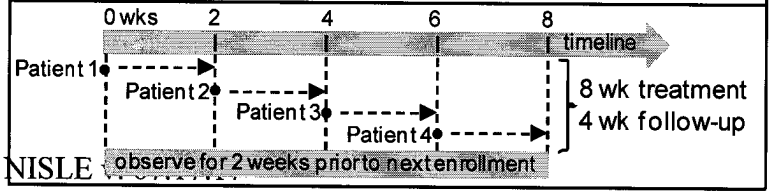
2. Secondary endpoints

a) Safety
Safety will be evaluated by determining the frequency of adverse events and serious adverse events including measurements of hematology, clinical chemistry, lipid profile and urinalysis parameters over the course of the study from baseline to day 56. Safety will also be determined by assessment of disease activity. All adverse events will be mapped into their MedDRA preferred terms and assessed according to criteria established by the National Cancer Institute—Common Terminology Criteria version 4 [NCI-CTCAE].

The Simon Two-Stage trial is an open-label trial with no placebo arm. We felt justified in including no placebo arm for the following primary reasons: (i) nelfinavir is safe and well-tolerated in HIV patients, (ii) after excluding subjects taking contraindicated medications, we have no reason to think that those enrolled will be at increased risk for toxicity to nelfinavir, (iii) we are dosing at or below the recommended dose of nelfinavir in HIV patients, (iv) we have carefully pre-determined stopping rules for toxicity, and (v) as an added immediate safety precaution, we will enroll the first four subjects sequentially with a 2 wk observation delay prior to enrolling the next subject.

To identify immediate unexpected toxicity issues, the first 4 subjects will be enrolled sequentially and each will be observed for 2 weeks prior to enrolling the next subject (Fig. 6). In all subjects, safety will be evaluated by the frequency of Adverse Events (AEs), serious AEs and changes in disease

Fig. 6: Immediate unexpected safety – *(1st 4 subjects)*



activity over the course of the study from baseline to day 56 (see Protections for Human Subjects section for more complete safety). We envision AEs to include both NCI-CTCAE grades and worsening of a subject's SLE (*e.g.*, a new BILAG A on the BILAG index) (see section 8.1 for definitions of AE's, SAE's and lupus disease flares). Clearly, AEs of the same type that are considered to be related to study therapy will elicit appropriate caution from the Safety Officer. Additionally, all subjects will be given investigator contact information for 24 hour use and, at each study visit, will be reminded to call study personnel to arrange for an "unscheduled" visit if they have concerns about their health.

While the Safety Officer has ultimate authority to address safety, we have established pre-determined stopping/pausing rules, as defined by the number and type of AEs (Table 1). These stopping rules comprise three levels of surveillance:

Table 1	Stopping Rules – DSMB
1st 4 subjects:	3 grade 3 or 4 AEs of same type 4 grade 3 or 4 AEs of any type
1st 13 subjects:	4 grade 3 or 4 AEs of same type 5 grade 3 or 4 AEs of any type
All 43 subjects:	10 grade 3 or 4 AEs of same type 15 grade 3 or 4 AEs of any type

(i) the first 4 subjects (Table 1, row 2)
(ii) the entire Stage 1 (first 4 plus next 9 subjects, Table 1, row 3) and
(iii) the overall trial (all 43 evaluable subjects, Table 1, row 4).

Enrollment will proceed only if these stopping rules have not been violated. In addition, protocol-specified requirements for the treatment of subjects will be discontinued for subjects under the following conditions: (i) at any time at the request of the subject, (ii) if the subject's health, safety, and/or well-being is threatened, (iii) if the subject requires an increase in dose of any concurrent SLE medications or experiences a grade 3 or higher NCI-CTCAE that is considered to be related to study therapy or (iv) if the subject becomes pregnant. Even though AE's may occur at any time in the 56 day treatment period, eligible subjects will continue to be enrolled regardless of how many subjects are still within the 56 day treatment and 28 day observation period. The rationale for this is that this is not a Phase I study and the study drug, nelfinavir, is FDA approved with a very good safety profile.

b) Disease activity

This study is exploratory and is not powered to adequately assess efficacy. However, we plan to enroll subjects with mild to moderate disease activity that, in the investigators opinion, will not require additional corticosteroids or immunosuppression for treatment of their disease activity. Five different assessments of disease activity are planned therefore we anticipate that we will be able to detect a trend for efficacy in those treated with nelfinavir. The potential effect of nelfinavir on clinical indicators of disease will be evaluated descriptively. Clinical indicators of disease will include:

- Changes in serum C3 and C4 complement levels from baseline to Day 56;
- Changes in serum CRP from baseline to Day 56;
- Changes in the SELENA SLEDAI score from baseline to Day 56;
- Changes in the PGA from baseline to Day 56;
- Changes in from baseline to Day 56;
- Changes in Joint Count from baseline to Day 56;
- Changes in BILAG scores from baseline to Day 56.

c) Health related quality of life

The potential effects of nelfinavir on patient quality of life will be assessed by changes in patient reported outcome measures from baseline to Day 56. The quality of life measures for this clinical trial include the following:

- The LupusPro Health Survey is a validated patient reported measure of functional health and well-being generalizable across ethnic backgrounds and gender [37].
- The patient global assessment scale is a 10 cm visual analogue scale with 1 mm increments from 0 through 100. 0 reflects no disease activity in the patient's assessment and 100 reflects maximum disease activity.

d) Interferon signature

Secondary analyses will explore the potential effect of nelfinavir on the expression of the IFN signature. Changes in expression of IFN inducible genes will be determined from baseline to Day 56. Expression of IFN inducible genes will be determined in two ways:

- Transfer of the IFN signature: as described previously [38], serum from SLE subjects will be incubated with normal PBMC and expression of IFN inducible genes will be measured using reverse transcriptase PCR.
- Microarray analysis: Expression of IFN inducible genes in peripheral blood will be measured by microarray analysis of RNA (extracted from whole blood in the PaxGene tubes) using the Illumina HT12v4 platform.

e) Cytokines

Changes in serum cytokine levels (IL-1, IL-6, and TNFα) from baseline to Day 56 will be determined for each treatment group at each dose level using ELISA assays in Dr. Diamond's laboratory.

f) SerologyAnticardiolipin Antibody Binding

Assessment of changes in autoantibody binding, including anti-Ro, La, Sm, RNP and cardiolipin antibodies, from baseline to Day 56 will be similar to the assessment of anti-dsDNA antibody binding. Investigators and study personnel will be blinded to autoantibody titers drawn during the course of the study. Blood obtained for the autoantibody titers will be spun and the serum stored at -20 or -80 degrees at each site on Days 1, 14, 28, 56 and 84. Frozen sera for the Central Laboratory for Days 1-56 will be sent overnight to the Coordinating Center following the Day 56 visit for each subject for determination of the primary endpoint. At study completion, all of the Day 84 Central Laboratory samples will be batched and sent to the Feinstein Institute. The samples will then be run simultaneously in the core laboratory in the North Shore/LIJ Health System.

6. STUDY WITHDRAWAL OR DISCONTINUATION

6.1 Discontinuation of Protocol-Specified Treatment Requirements

A subject is considered to have completed the study when he/she has completed the Day 84 visit. Protocol-specified requirements for the treatment of subjects will be discontinued for subjects under the following conditions:

1. Any protocol-specified treatment requirement will be discontinued immediately at any time during the study at the request of the subject.
2. Investigator will discontinue any protocol-specified treatment requirement if the subject's health, safety, and/or well-being is threatened.
3. Protocol-specified treatment requirements will be discontinued and replaced with appropriate therapy for any subject who experiences or requires any of the following:

- An increase in dose of any concurrent SLE medications (including but not limited to corticosteroids, immunosuppressives, and/or immunomodulatory medications such as azathioprine, methotrexate, leflunomide, mycophenolate, and/or hydroxychloroquine) or addition of a new immunosuppressive medication (including cyclophosphamide or rituximab). *Note:* corticosteroids may be increased for a maximum of 2 days for reasons unrelated to SLE disease activity provided the last dose is taken more than 5 days prior to the day 56 assessments (section 5.3)
- A grade 3 or higher NCI-CTCAE (version 4.0) adverse event that is considered to be related to study therapy during the course of the study. The exception to this will be hemoglobin levels where a grade 3 level of 8 may be acceptable. This will depend on the hemoglobin level at study entry and the investigator's assessment of relationship to study drug. A requirement for blood transfusion would be considered a stopping point.
- Pregnancy
- If a subject enrolls in a concurrent interventional trial.

In addition, subject non-compliance with treatment regimens or failure to keep appointments may disrupt protocol-specified treatment requirements and necessitate permanent discontinuation of treatment procedures at the discretion of the investigator.
Finally, protocol specified treatment requirements will be discontinued as a natural consequence in subjects who are withdrawn from the study per the study guidelines.

6.1.1 Procedures for Discontinuation of Protocol –Specified Treatment Requirements and Follow-Up

For subjects who have been discontinued from protocol-specified treatment requirements but have not withdrawn consent, the following procedures will apply:

1. The subject will be asked to complete a discontinuation visit at the time of study discontinuation that will include a physical exam, lupus disease assessments as applicable (SLEDAI, BILAG, joint count), SLICC, LupusPRO, PGA, cbc, chemistry, C3, C4, anti-dsDNA and mechanistic studies.
2. If discontinuation is due to safety concerns, the subject will be given appropriate care under medical supervision, until the symptoms of any adverse event resolve or the subject's condition becomes stable.

6.2 Subject Withdrawal from the Study

When a subject is withdrawn from the study, protocol-specified treatment requirements are discontinued, and study-related visits, exams, procedures, assessments, tests and data collection are terminated. Individual subjects will be withdrawn from the protocol under the following conditions:

1. The subject withdraws consent.
2. The investigator believes it is in the best interest of the subject.
3. Subjects who are lost to follow-up will also be regarded as withdrawn from the protocol.

7. STATISTICAL ANALYSIS

7.1 Statistical Methods

The statistical analyses (*i.e.*, decision rules) have already been described above. In brief, we are testing the hypothesis that H_0: response rate is <20% vs. H_A: response rate is ≥40% using a Simon Two-Stage optimal design [39]. Stage 1 will enroll 13 subjects; if 3 or fewer respond, then the trial is stopped due to an inadequate response rate. If 4 or more subjects respond, then the trial continues to Stage 2, where 30 additional subjects are enrolled (total n=43). At the end of Stage 2, if 12 or fewer of the 43 subjects respond, then the treatment is declared inadequate. If at any point 13 or more subjects have responded, then the treatment will be considered for further testing. The procedure uses alpha=0.05 and beta=0.20. Under H_0, the expected sample size is 20.6 and the probability of early termination is 75%. In order to operationalize the Simon Two-Stage rules, we will sequentially analyze and accumulate results on individual subjects as they complete Day 56 of the treatment period. Specifically, if 4 or more subjects have responded at any point in Stage 1, we will begin enrollment for Stage 2. Once a total of 13 subjects have responded the study will terminate.

7.1.1 Handling of Dropouts and Non-Evaluable Subjects

For the evaluation of efficacy using the Simon Two-Stage Optimal Design rule, any subject who is not evaluable or drops out from the study for any reason (including adverse events), will be replaced by a new subject. The subject being replaced will not be used in the analysis of efficacy. As noted elsewhere in this protocol, a subject will be considered "evaluable" for efficacy if he/she has complied with at least 80% of the prescribed medication dosing over the entire 56 days of medication administration (<80% is "not evaluable"). This "per protocol" rule has been implemented since this is a Phase II efficacy trial and the "intention-to-treat" principle does not apply. In order to account for a standard dropout rate of 20%, the potential maximum number of subjects to be enrolled will increase to 51 subjects.

For the evaluation of safety, any subject who is exposed to at least one dose of the medication will be included in all analyses of adverse events, even if this subject is replaced under the efficacy rule cited above.

The statistical analysis for the primary endpoint, therefore, is a straightforward calculation of percent change within each subject in anti-dsDNA antibody titer from baseline to 8 weeks. We have defined a clinically meaningful decrease in anti-dsDNA antibody titer to be a decrease in titer that is ≥ 35%; this is based on serologic data from a previous study comparing the efficacy of prednisone compared to placebo for disease flare prevention in serologically active, clinically stable SLE subjects [39]. For other secondary endpoints, descriptive statistics on continuous

measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

8. SAFETY MONITORING AND REPORTING (please also reference the Data Safety Monitoring Plan and sections 3.n-3.o of the MOOP)

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording and reporting that data. Serious adverse events and events requiring expedited review must be reported promptly (within 24 hours of the participating site PI becoming aware of the event) to the Sponsor Site PI and IND sponsor (Dr. Meggan Mackay, FIMR) who will inform the Safety Officer (SO) and NIAMS (through the KAI) within 48 hours. IND safety repots will be distributed to the participating site PIs and regulatory authorities (FDA) within 15 days. It is the Sponsor Site PI's responsibility to inform the Sponsor Site IRB at the FIMR. IRB reporting of SAEs and AEs will also be done as locally mandated. Information in this section follows guidelines and definitions from FDA-*CFR Code of Federal Regulations Title 21, Part 312 Investigational New Drug Application* found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm. Data for this study will be collected on paper Case Report Forms (CRFs) that will be transmitted electronically to a central web based platform overseen by the Biostatistics Unit at the FIMR. Access to the database is restricted to the protocol Chair, Sponsor site PI and the personnel designated as data entry. The Co-Investigators, CSC, Office of Research Compliance and biostatisticians will have read only access. The web-based system is HIPAA compliant with strict password control and an automated database audit system.

The Office of Research Compliance (ORC) of NS-LIJ HS will be responsible for monitoring the study sites. The Sponsor site PI, Dr. Mackay, and the Steering Committee, comprised of Drs. Mackay, Aranow, Diamond and Coleman and Joanna Stein from the Biostatistics Unit, will oversee the conduct of the study. Principal Investigators at participating sites may also be part of the Steering Committee.

8.1 Definitions

For consistency of labeling and categorizing adverse events, the Food and Drug Administration (FDA), Code of Federal Regulations (CFR) title 21, part 312 Investigational New Drug Application – safety report guidelines, April 1, 2013 will be used in this study. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.0 will be used for grading of adverse events in this study. NCI CTC Version .0, DCTD, NCI, NIH, DHHS; June 14, 2010, publish date: May 28, 2009 (http://ctep.cancer.gov).

Adverse event: An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It

does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, 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 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 patient or 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 an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Lupus Flare
A lupus flare is any significant worsening of the signs, symptoms and laboratory test abnormalities associated with lupus. These changes are captured and graded in the BILAG 2004 and will be considered part of the safety information for this study. The details of the BILAG grading system are provided in appendix A. In general, the following approach is used:

- Mild lupus flare (Grade 1): New BILAG 2004 grade C in one or more organ systems.
- Moderate lupus flare (Grade 2): New BILAG 2004 grade B in one or more organ systems.
- Severe lupus flare (Grade 3): New BILAG 2004 grade A in one organ system.
- Life-threatening or disabling lupus flare (Grade 4): A life-threatening or disabling new BILAG 2004 grade A.

Signs, symptoms and laboratory test abnormalities reported as part of a lupus flare will not be separately reported as an adverse event using the FDA-*CFR Code of Federal Regulations Title 21, Part 312 Investigational New Drug Application definitions.*

8.2 Collection and Recording of Adverse Events

8.2.1 Collection Period

Adverse events will be collected from the time of initiation of study intervention (i.e., the first dose of study drug) until he/she completes study participation on Day 84 or until 30 days after he/she prematurely withdraws from the study. In the event of an adverse event, the first concern will be for the safety of the patients. Investigators are required to collect and document all adverse events (AEs).

8.2.2 Collection of Adverse Events
Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Questioning the subject in an objective manner.
- Receiving an unsolicited complaint from the subject.

In addition, an abnormal value or result from a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, or an electrocardiogram) can also indicate an adverse event. If this is the case, then the evaluation that produced the value or result should be repeated until that value or result returns to baseline or can be explained and the subject's safety is not at risk. If an abnormal value or result is determined by the investigator to be clinically significant or NCI CTCAE Grade 1 and above, it must be recorded as an adverse event. Once recorded, an AE will be followed until it resolves with or without sequelae, or becomes medically stable.

8.2.3 Recording Adverse Events
Throughout the study, the investigator will record and grade adverse events on the appropriate AE case report form (AE CRF) regardless of their severity or relation to study medication or study procedure. All requested information on the AE CRF should be provided, if available.

8.2.4 Recording Serious Adverse Events
Serious AEs will be recorded on the appropriate SAE CRF. All requested information on the SAE CRF should be provided, if available.

8.3 Grading and Attribution of Adverse Events

8.3.1 Grading Criteria
The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version (NCI CTCAE) 4.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. Note: all adverse events are to be reported and graded, whether or not related to disease progression or intervention.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.
Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.
Grade 4 = life-threatening or disabling adverse event.
Grade 5 = death.

8.3.2 Attribution Definitions
The relation, or attribution, of an adverse event to an investigational product will be determined by the site investigator. The site investigator will also record the determination of attribution on the appropriate CRF and SAE reporting form. The relation of an adverse event to the study intervention will be determined using the following descriptors and definitions:

- Unrelated: The adverse event is clearly not related to the investigational agent(s).
- Unlikely: The adverse event is doubtfully related to the investigational agent(s).
- Possible: The adverse event may be related to the investigational agent(s).
- Probable: The adverse event is likely related to the investigational agent(s).
- Definite: The adverse event is clearly related to the investigational agent(s).

8.4 Reporting of Adverse events
All patients who receive at least one dose or part of a dose of the trial medication and complete a safety follow-up, whether withdrawn prematurely or not, will be included in the safety analyses. All data relating to safety will be listed and summarized separately for the treatment period and for the entire study.
All safety reports will be reviewed by the Sponsor Site PI, Dr. Mackay, and the Steering Committee in addition to the Safety Officer appointed by NIAMS.

8.4.1 Adverse Events Requiring Expedited Reporting
The following Adverse Events, as graded with the NCI CTCAE manual version 4.0 will be reported in an expedited fashion by site investigators to the Sponsor site PI, Dr. Mackay, regardless of expectedness or relationship to study intervention:

- All life threatening and serious adverse events
- All NCI CTCAE Grade 4 events
- All NCI-CTCAE Grade 3 events
- Occurrence of BILAG A

The Sponsor Site PI, Dr. Meggan Mackay, will report all expedited reports (including life threatening events, SAEs, protocol deviations affecting participant safety and/or lab values reported as Grade 3 or 4 events) within 48 hours of becoming aware of the event to NIAMS and the independent SO through the Executive Secretary, KAI (please refer to the Data and Safety Monitoring Plan, DSMP). Dr. Mackay will also forward all expedited reports to members of the Steering Committee.

8.4.2 Reporting Timeline
The following process for reporting a serious adverse event, or an event requiring expedited reporting, ensures compliance with the ICH guidelines and the Food and Drug Administration (FDA) regulations. Please also reference the DSMP for additional clarification. When a participating investigator identifies a serious adverse event or other adverse event requiring expedited reporting or pregnancy, he or she must notify the Sponsor site PI, Dr. Meggan

Mackay, directly within 24 hours of discovering the event, and complete/fax the Serious Adverse Event form within 1 business day. Dr. Mackay will notify the Steering Committee and is responsible for notifying the sponsor site IRB as per regulatory requirements. Dr. Mackay will also notify the independent SO and NIAMS through the Executive Secretary, KAI within 48 hours of becoming aware of the event.. Dr. Mackay currently holds the approved IND for this study. All IND reports for SAEs/expedited reports will be sent to the FDA and all participating site PIs no later than 15 days after the Sponsor Site PI determines that the information qualifies for IND reporting according to the FDA-*CFR Title 21, Part 312 Investigational New Drug Application* guidelines.

A listing of all AEs will be compiled by the Biostatistics Unit every 6 months and submitted to the Sponsor Site PI, members of the Steering Committee, the SO and NIAMS for review.

8.4.3 Reporting of Adverse Events to Local IRBs
All investigators must report adverse events to their respective IRBs as locally mandated by them. SAEs that are determined by the study sponsor (Dr. Mackay) to warrant a Safety Report to the FDA will also be distributed to all participating institutions for IRB submission (section 8.4.2).

8.4.4 Safety reports to the FDA and participating investigators
Safety reports will be submitted to the FDA and participating investigators by the study sponsor (Dr. Mackay) in accordance with applicable regulations (21 CFR 312.32) and ICH guidelines. Safety reports of potential serious risks will be distributed as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for the reporting under the following paragraphs (8.4.4a, 8.4.4b, 8.4.4c and 8.4.4d):

a) *Serious and unexpected suspected adverse reaction.* Any suspected adverse reaction that is both serious and unexpected. Suspected adverse reaction will be reported only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
   (i) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
   (ii) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
   (iii)An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

b) *Findings from other studies.* Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.

c) *Findings from animal or in vitro testing.* Any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans

exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.

d) *Increased rate of occurrence of serious suspected adverse reactions*. Clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

8.5 Pregnancy Reporting

This study includes pregnancy information as safety data. Information about any pregnancy should be reported promptly to the sponsor on the same timeline as a SAE. All pregnancies identified during the study must be followed to conclusion and the outcome of each must be reported. The investigator should be informed immediately of any pregnancy in a study subject or a partner of a study subject. A pregnant subject should be instructed to stop taking study medication. The site investigator should report to the Sponsor site PI, Dr. Mackay, at the FIMR all pregnancies within 1 business day using the Pregnancy Monitoring form. The site investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Nelfinavir has a pregnancy risk factor Category B; no evidence of human risk in controlled studies. Nelfinavir crosses the placenta and no increased risk of overall birth defects following first trimester exposure in humans has been reported to the antiretroviral pregnancy registry. Nelfinavir is recommended for use in HIV + women for prohoylaxis of perinatal transmission if alternative regimens are not tolerated. Monitoring of the pregnant subject should continue until the conclusion of the pregnancy, and a follow-up Pregnancy Monitoring form detailing the outcome of the pregnancy should be submitted to the Sponsor site PI, Dr. Mackay. When possible, similar information should be obtained for a pregnancy occurring in a partner of a study subject. Information requested about the delivery will include:

- Subject's enrollment ID
- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

Should the pregnancy result in a congenital abnormality or birth defect, an SAE also must be submitted to the Sponsor site PI, Dr. Mackay, using the SAE reporting procedures described above.

8.6 Reporting of Other Safety Information

An investigator should promptly notify the Sponsor site PI, Dr. Mackay, when an "unanticipated problem involving risks to subjects or others" is identified which is not otherwise reportable as an adverse event.

Unanticipated problems will be defined according to guidelines by the Office for Human Research Protection (OHRP) (http://www.hhs.gov/ohrp/policy/advevntguid.html and includes any incident, experience, or outcome that meets all of the following criteria:

a. unexpected (in terms of nature, severity, or frequency) given (i) the research procedures that are described in the protocol and informed consent document; and (ii) the characteristics of the subject population being studied;

b. related or possibly related to participation in the research (reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.7 Review of Safety Information

8.7.1 Routine Review by the Steering Committee
The Biostatistics Unit will generate reports that compile all newly submitted and accumulated AEs, SAEs, toxicities, pregnancies, and concomitant medications every 6 months. Subsequent review of periodic reports will be performed by members of the Steering Committee, the SO and NIAMS. In addition, the Steering Committee will receive SAE and pregnancy reports for review from the participating sites.

8.7.2 Safety Officer Review (please refer to Appendix C of the Data Safety Monitoring Plan)
The Safety Officer will review accumulating safety data every 6 months. Events requiring expedited review will be reviewed by the SO and in a timely manner as outlined above and in the DSMP. All SO reviews will be reported to NIAMS and to the Sponsor site PI, Dr. Mackay.

9. ACCESS TO SOURCE DATA AND DOCUMENTS

Each participating site will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects participating in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, each site must permit authorized representatives of the IND sponsor (Dr. Mackay), the Office of Research Compliance (ORC) and Biostatistics Unit at the FIMR and regulatory authorities to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, monitoring, audits, and evaluation of the study safety and progress. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. Participating sites will normally be notified in advance of auditing or monitoring visits.

All subject records and study documentation will be kept as per institutional policy and regulatory requirements after the protocol is completed. This will include all documentation of AEs, records of study drug receipt and dispensation, and all IRB correspondence. All study

records will be kept for at least 2 years after the marketing application is approved; or if an application is not filed/approved, until 2 years after the investigation is discontinued and the FDA has been notified.

10. DATA COLLECTION, QUALITY CONTROL AND QUALITY ASSURANCE MONITORING

The site investigators are required to keep accurate records to ensure the conduct of the study is fully documented. The period of record retention should be consistent with the record retention policies of the sponsoring agency or applicable regulatory agencies.

The site investigators will report all protocol deviations (including those found by study monitors) to their IRBs as per their policies and to the sponsor as applicable. The investigator will forward reports of protocol deviations to the Steering Committee for review for potential impact on evaluations of safety and efficacy and these will be submitted to the North Shore-LIJ IRB as appropriate.

The Office of Research Compliance (ORC) will provide clinical research monitoring services for all subjects to be enrolled in this protocol at all participating sites. The ORC is responsible for monitoring the conduct of the trial, for verifying adherence to the protocol, and data quality through confirming the completeness, consistency and accuracy of all documented data. Monitoring will be done remotely or on site as needed.

Data at the clinical sites will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, and clinical subject charts. Data from these source materials will be recorded on CRFs and transmitted to the Biostatistics Unit at the FIMR. Laboratory data from each site will be recorded on the CRFs. All CRFs will be transmitted to the Biostatistics Unit at the FIMR on a regular basis following completion of each study visit. Data will be compiled and stored in a computerized central web-based database in the Biostatistics Office at the FIMR. The data will be further validated via a series of manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed and any resulting queries will be resolved with the investigators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations. The DSMP contains additional guidelines for data collection and monitoring.

10.1 Monitoring Plan

Monitoring services by the ORC at each participating site will be performed according to the established monitoring plan. Clinical research monitoring services for all subjects to be enrolled in this protocol at the FIMR and other participating sites (to be named) to include the general areas:

- Good Clinical Practice Regulatory Review

- Patient Case Review of Critical Study Data and Processes Including:
  - Case Report Form Completion and Source Document Verification
  - Protocol and Informed Consent Compliance
- Protocol Drug Accountability

In addition the ORC will provide regulatory consultative services to the central study coordinator and training in Good Clinical Practice (GCP) requirements for all participating site personnel.

10.1.1 Monitoring Review Schedule

The ORC will provide monitoring services to assess performance at each site at a minimum of 3 visits (1-2 days) per site:

- Site initiation visit: Prior to study start-up for GCP and protocol overview
- Follow-up monitoring visits: occurs annually with the frequency outlined in the monitoring plan as long as the site continues to enroll subjects. However additional visits may be performed for targeted reviews as required.
- Final monitoring visit: Study close out

Monitoring visits will be done on-site or remotely, as indicated.

10.1.2 Monitoring Reporting

Regular monitoring reports will be generated by the ORC after each review and will be provided to both the performance site and the Sponsor site PI and data-coordinating center. Resolution of queries and outstanding issues or concerns will be the responsibility of the individual performance site, PI, and Data Coordinator.

The Sponsor site PI will be responsible for reporting incidents of IRB non-compliance to the North Shore-LIJ Health System IRB (in compliance with regulations on the protection of human subjects and institutional policy and procedures) and responsible for securing compliance at all trial sites.

11. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

The study will be conducted according to Good Clinical Practice (GCP) guidelines, the Manual of Procedures (MOP), U.S. 21 CFR Part 50 – Protection of Human Subjects, 21CFR312 subpart D and Part 56 – Institutional Review Boards.

11.1 Compliance with Good Clinical Practices

This trial will be conducted in compliance with the protocol, current GCPs recommended by the International Conference on Harmonization (ICH) and the applicable regulatory requirements for participating institutions. These include the tenets of the Declaration of Helsinki and review and approval by the appropriate ethics review committee or IRBs of participating organizations. FIMR shall monitor the progress of the clinical investigations being conducted under its IND through monitoring services provided by the ORC.

11.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and associated informed consent documents by an appropriate ethics review committee or IRB. Any amendments to the protocol or consent materials must be approved before they are placed into use. In both the United States and in other countries, only institutions holding a current Federal Wide Assurance issued by the Office of Human Research Protection (OHRP) at the Department of Health and Human Services (DHHS) may participate.

The investigator will inform the IRB of serious or unexpected AEs that might occur during the study and are likely to affect the safety of the subjects, or the conduct of the study. The investigators will comply fully with all IRB requirements for both the reporting of AEs, protocol or consent form changes, as well as any new information pertaining to the use of the study medication that might affect the conduct of the study.

11.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki, as well as compliance with all IRB requirements, will be implemented in the study, before any protocol-specified procedures are carried out. A standard consent form for subject participation will be provided with the protocol to each institution. Any modifications to the standard information in the template will require review and approval by the sponsor. Informed consent will be obtained in accordance with 21 CFR 50.52. Information may be given to subjects in oral, written or video form by the investigator. All prospective subjects will be given ample time to read the consent form, and ask questions, before signing.

If subjects are to be enrolled who with limited English proficiency, the consent materials must be translated into the language appropriate for the enrolling subject or a short form authorized by the IRB in the appropriate language should be used. Translated documents must be certified to contain the complete descriptions provided in the English version of the document. If an interpreter is used to provide or assist in describing the consent materials to an enrolling subject, the interpreter must also sign the consent materials certifying their involvement with the consent process. In the event that a telephone interpreter is used, the interpreter number and name of the interpreter service should be documented.

After completion, a copy of the signed consent form will be given to the subject. The original signed consent form will be kept on file in the subject's study chart, available for inspection by regulatory authorities, both federal and institutional.

11.4 Safety Officer

The responsibility for reviewing the ethical conduct of the study and for monitoring reports of evidence of adverse or beneficial effect is assigned to the independent Safety Officer (SO). The SO is an independent advisor appointed by NIAMS who will be responsible for continuing

review of study information. The SO makes recommendations to the NIAMS and to the FIMR on issues affecting the course and conduct of this clinical study (see also section 8.7.2 and sections 4-6 of the DSMP).

12. STUDY MONITORING AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

This study will be monitored according to Good Clinical Practice (GCP) guidelines, 21 CFR Parts 312.50.

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