ATTACHMENT 1

PROTOCOL

Clinical Trial of Topical Thalidomide for Oral Lesions of HIV/AIDS

Precis

This clinical trial will evaluate the efficacy of topically-applied thalidomide as a treatment for painful oral lesions in patients infected with the Human Immunodeficiency Virus (HIV). Thalidomide given orally (PO) is effective for aphthous ulcers in HIV seropositive as well as immunocompetent patients. However, its utility has been limited by a spectrum of adverse effects. The combination of lack of tolerability for PO thalidomide, its teratogenicity, and reported increases in viral load have raised concerns regarding use of this drug in HIV-infected patients. Given the growing numbers of patients with HIV infection and the absence of other effective treatments for these painful and debilitating ulcerations, the need exists to develop alternative treatment strategies. Topical drug administration is a strategy for enhancing absorption at the anatomical target site while lowering plasma drug concentrations, hence decreasing the potential for toxicity.

When given PO, thalidomide takes four to six weeks to reach sufficient tissue concentrations to promote ulcer healing. However, we have demonstrated efficacy for healing as well as pain reduction for 20 mg topical thalidomide in a mean of 17 days, with minimal systemic absorption and adverse effects. These data suggest that topical administration produces high local tissue concentrations which cannot be achieved with PO administration without dose-limiting adverse effects. This study is a phase II/III multi-center clinical trial for the treatment of aphthous ulcers of HIV/AIDS using a topical thalidomide formulation. The predicted outcome is that a topical route of administration for thalidomide will result in lesion healing and diminution of pain, without the adverse effects inherent in the higher systemic (PO) dose. Moreover, demonstration of a therapeutic effect or reduced toxicity will provide a basis for the further development of this formulation for the treatment of immune-related mucosal ulcers of other idiopathic ulcerative conditions.

1.0 Introduction

Oral manifestations of HIV disease have been recognized since the onset of the HIV pandemic and are important indicators of the natural history of the disease, as shown by their inclusion in staging systems such as the Walter Reed Staging Classification (Redfield 1986) and the system used by the Center for Disease Control and Prevention (CDC) (CDC 1993). Oral signs and symptoms are also indicators of prognosis (Dodd, 1991; Greenspan, 1991; Katz, 1992; Glick, 1994; Grbic 1995) because they are positively associated with CD4 counts and viral load (Barr, 1992; Banqui 1999). The most common oral mucosal manifestations of HIV are candidiasis, hairy leukoplakia, periodontal disease, Kaposi's sarcoma, recurrent herpes simplex virus (HSV), and recurrent aphthous ulcers (Melnick, 1989, Greenspan, 1990). Prior to the introduction of combination therapy for treatment of HIV, it was estimated that up to 90 percent of HIV-infected persons would experience at least one oral manifestation during the course of the disease (Moniaci, 1990, Barr, 1992, Laskaris, 1992) and up to 50 percent would experience oral ulcerations (Greenspan, 1992). Since the introduction of combination therapy for HIV, a decrease in opportunistic oral infections, such as candidiasis, oral hairy leukoplakia, kaposi's sarcoma, and HSV has been noted, and is attributed to lower viral load and higher CD4 counts secondary to the use of combination anti-retroviral therapy (Mellors, 1997; Mirowki, 1998; Banqui, 1999; Greenwood, 2002; Patton, 2000). Although the prevalence of infectious oral manifestations has been reduced, specific reductions in aphthae have not been formally reported.

National surveillance data from the CDC indicate that the decline in HIV incidence noted in the 1990's has slowed. This increased incidence of HIV combined with the decline in deaths due to AIDS translates into a higher AIDS prevalence (CDC, 2001). These data, combined with the lack of prophylaxis for HIV infection and its progression to AIDS, has contributed to the prediction that the numbers of persons living with HIV/AIDS will continue to increase over the next several years (CDC, 2001). Data from the oral health component of the national HIV Cost and Services Utilization Survey, a probability sample of 2,889 HIV+ individuals, gives a population estimate of 54,000 HIV+ persons reporting oral pain in the past 6 months. Approximately a third of respondents with oral pain reported experiencing oral lesions (Garcia, unpublished observations 2001), with 38 percent describing their lesion as a "painful ulcer". A separate study in a large clinical sample (n = 245) of patients with HIV/AIDS showed that self-diagnosis of intraoral ulcers had a moderate kappa agreement of 0.41 between patient and dentist (Patton, 2001), giving credence to the validity of self-report of oral ulcers. Although the types of oral ulcers reported in these studies were not defined, studies of prevalence in clinical populations report aphthous ulceration in 15 to 31 percent of HIV-infected patients (Pindborg, 1989; Connolly, 1989).

Recurrent aphthous ulcers are one of many different types of oral lesions which can result in the condition called stomatitis. Stomatitis is defined as inflammation of the mucous membranes of the oral cavity and oropharynx, which may range from redness to ulceration (Hyland, 1997). Stomatitis is a clinical presentation rather than a discrete entity. Aphthous, from the Greek "white blister", is defined as "recurrent small painful ulcer(s) of unknown etiology on a mucous membrane; (plural 'aphthae')"; "stomatitis of unknown etiology characterized by intermittent episodes of painful ulcers" (Stedman's Medical Dictionary, 2000). Ulcers of similar characteristics and also of unknown etiology may manifest in gastrointestinal, vaginal, and rectal mucosa and may also be referred to as aphthae or aphthous-like (Bach, 1988, 1990). Commonly referred to as "canker sores", aphthous ulcers have a diverse nomenclature: "Sutton's disease" (Sutton, 1911), "aphthous stomatitis", "minor and major aphthae", "herpetiform ulceration", and "recurrent aphthous ulcers" or "RAU" as first termed by Shafer (1983). For brevity, the acronym RAU is used throughout the remainder of this protocol to refer to recurrent aphthous ulcers.

RAU are not uncommon in the U.S. population, occurring with a prevalence of up to 20 percent. They usually spontaneously resolve within three to fourteen days (Embil, 1975). In comparison, the reported prevalence of RAU ranges from 15 to 31 percent in HIV seropositive patients (Pindborg, 1989; Connolly, 1989). Although it is not certain whether RAU occurs more frequently in HIV-infected individuals, the lesions are larger and more prolonged (Ficarra, 1995). Further, pain associated with these lesions adds substantial morbidity to HIV disease (Bach, 1988; Ghigliotti, 1993). The prolonged duration of these lesions and associated oral pain may lead to weight loss from decreased ability to eat (Greenspan, 1990; Gilmore, 1995; Jacobson, 1997), which is compounded by weight loss due to cachexia (Klausner, 1996; Reyes-Teran, 1996). There are no satisfactory therapies or accepted standards of care associated with aphthous ulceration in patients with HIV/AIDS.

The lack of effective treatments for persistent aphthae in HIV/AIDS continues to motivate research directed towards the discovery of treatment strategies. Thalidomide has proven effective in controlled clinical trials at a dose of 200 mg PO daily. However, its utility is hampered by a high incidence of adverse effects and safety concerns in the setting of HIV/AIDS, e.g, a high incidence of

side effects (55 percent) and a high drop-out rate (20 percent), as well as unexpected increases in viral load (Jacobson, 1997). Given the growing numbers of patients with HIV infection and the absence of other effective treatments for these painful and debilitating ulcerations, the need exists to develop alternative treatment strategies. When given PO, thalidomide is reported to need four to six weeks to reach sufficient tissue concentrations to promote oral ulcer healing (Chen, 1989; Simmons, 1997; Revuz, 1990; Jacobson, 1997 and 2001). However, there is evidence that lesions can heal more rapidly with topical thalidomide application. A mouse-dermis model demonstrated lesion healing within less than a week (Piacquadio, 1995), and we have demonstrated a dose-related therapeutic effect with minimal adverse effects using a topical thalidomide preparation for aphthous ulcers of HIV/AIDS. These data provide a basis for dose selection and the further testing of topical thalidomide for the treatment of painful aphthous ulcers associated with HIV infection.

Drug development, formulation, and phase I-II dose-finding have been conducted in the Oral Infection and Immunity and the Pain and Neurosensory Mechanisms Branches in the Division of Intramural Research, NIDCR in collaboration with the NIH Clinical Center Pharmaceutical Development Service. An FDA-approved IND is in place to conduct the proposed study. The proposed trial is the next logical step in demonstrating efficacy and safety of topical thalidomide for aphthous ulcers associated with HIV/AIDS.

2.0 Objectives

The purpose of the present study is to assess the efficacy and safety of a novel topical thalidomide formulation for healing of painful oral lesions diagnosed as RAU in patients with HIV/AIDS. No safe, effective treatment is currently available for the management of these lesions secondary to HIV infection. These ulcers can be very debilitating due to the long duration, intense pain, and difficulty in swallowing with resultant decreased nutritional intake in a population already at risk for physical wasting associated with the disease process.

Outcome measures to be evaluated at baseline and over time include: size of the intraoral lesion(s), the sensory component of pain, analgesic usage, and the incidence of self-reported side effects. Specific objectives to be achieved by the proposed investigation are:

2.1 To document the size, duration and painfulness of the lesion(s) at baseline and weekly for up to four weeks or until the lesion has healed, whichever occurs soonest.

Hypothesis 1: 20 mg topical thalidomide will demonstrate superiority for healing of aphthous ulcers associated with HIV/AIDS compared to placebo vehicle, as measured by change in lesion size and healing rate (days to healing).

- Healing is defined as closure or near closure of the edges of the lesion and/or granulation. Healing will be quantified by 1) a blinded, calibrated examiner, and 2) a second blinded observer using intraoral photographs taken at weekly intervals for measurement of size.

Hypothesis 2: 20 mg topical thalidomide will demonstrate greater ulcer-associated pain reduction compared to placebo vehicle, as measured by pain reduction from study entry to end of study

- The sensory component of pain will be measured using 4-point category scale and 100 mm visual analogue scale (VAS). Magnitude of change in pain report from baseline to end of study will be evaluated by patient report.

2.2 To assess the incidence of adverse effects associated with study participation.

2.3 (In a subset of patients) To measure blood levels of topical thalidomide.

2.4 (In a subset of patients) To measure levels of TNF-α in circulation and locally at the lesion site at baseline and over time.

The primary outcome measure is healing and the secondary outcome measure is pain reduction.

3.0 Background

As described in the *Introduction*, mucosal lesions of unknown etiology, such as RAU, are often unresponsive to standard therapies in patients with HIV/AIDS, causing substantial morbidity. The literature for RAU suggest that the inflammatory response contributes to the pathogenesis of RAU. However, the contribution of cytokines to this mucosal immune response in humans remains largely unknown. The drug thalidomide demonstrates inhibition of the pro-inflammatory cytokine TNF-α *in vitro*, and has been shown to be effective for RAU in HIV-infected patients (Revuz, 1990; Jacobson, 1997, 2001).

3.1 TNF-α and RAU

Cytokines produced by infiltrating inflammatory cells perpetuate the process of inflammation and tissue destruction. TNF-αfirst described by its apparent ability to cause tumor necrosis (Old, 1985), is a multifunctional cytokine primarily secreted by monocytes and macrophages, but also by mast cells, epithelial cells, keratinocytes, fibroblasts, and T-cells (for review see Vilcek, 1992**;** Baud, 2001). TNF is synthesized as a membrane-bound pro-protein, cleaved by the metalloprotease TNF-α converting enzyme to yield TNF-α as a soluble protein of approximately 17 kDa, which combines to form a 51 kDa trimer, the active form of the TNF-α ligand (Aggarwal, 1985; Smith, 1987). TNF homotrimers induce signaling by aggregation on transmembrane receptors (Engellman 1990), a 55 kDa protein (p55) and a 75 kDa protein (p75), known as TNF receptors (TNFR) 1 and 2, respectively (Hohmann, 1989; Brockhaus, 1990) and more recently renamed as TNFRSF1A and B (http://www.gene.ucl.ac.uk/nomenclature/). Receptor binding results in cross-linking and signal transduction (Pennica, 1992; Flier, 1996; Tchoukalova, 2001). However, the receptors also act as endogenous antagonists for TNF-α in their soluble forms by binding TNF-α and preventing its action on cellular targets (Mohler, 1993; Evans, 1994).Cleavage by protein kinase C at the membrane surface releases soluble binding proteins that increase the activity of TNF-α at low concentrations and inhibit TNF-α activity at high concentrations (Gatanaga 1990; Lantz, 1990; Olsson, 1993).

In addition to its function in tumor cell cytotoxicity, TNF-α has a broad spectrum of activity which classifies it as a pro-inflammatory cytokine (for review, see Vassalli, 1992 and McDermott, 2001). Among these activities are: increased expression of adhesion molecules and regulation of chemotaxis and adhesion to endothelial cells (Barker, 1990; Thornhill, 1991; Griffiths, 1991);

induction of cytokine secretion and apoptosis; and activation of leukocytes, such as T- and B-cells, macrophages, granulocytes, neutrophils, and endothelial cells (Sampaio, 1991**;** Moreira, 1993; Forsberg, 2001; Jablonska, 2001).

Clinically the effects of excess TNF-α result in pyrexia, cachexia , and tissue injury (Piguet, 1990; Rai, 1997). Accordingly, TNF-α is implicated in the pathogenesis of several inflammatory diseases and conditions, including sepsis (Tracey, 1986), inflammatory bowel disorders (Kucharzik, 1997; Targan, 1997), periodontal disease (Assuma, 1998, Salvi, 1998), TRAPS (Toro, 2000), and rheumatoid arthritis (Bertolini, 1986; Moreland, 1997). TNF-α has also been found to be increased in PBMCs of patients with RAU (Taylor, 1992). TNF-α is also elevated in HIV disease (Lahdevirta, 1988; Kobayashi, 1990), which may account for some of the clinical manifestations of HIV/AIDS such as fevers and wasting (Talal, 1992; Farber 1993; Espinoza, 1992), and may also contribute to HIV replication and increased viral load. Soluble TNFR1 and 2 are present in serum from the early onset of HIV infection and have been proposed as secondary markers of disease progression (Fahey, 1998; Godried, 1994; Hober, 1996, Rimaniol, 1996).

Pro-inflammatory cytokines have been associated with cutaneous lesions, such as actinic prurigo, a condition in which TNF-α is co-localized with keratinocytes in biopsy specimens (Arrese, 2001). Elevated TNF-α has been demonstrated in colonic biopsies from intestinal mucosa in inflammatory bowel disease and associated with mononuclear cells in the lamina propria (Reinecker, 1993). TNF-α has also been associated with skin and peripheral nerve pathology in patients with leprosy (Khanolkar-Young, 1995). Analysis of serial biopsies of cutaneous lesions of leprosy showed ribonucleic acid (RNA) message for TNF-α during the reactive phase (Moraes, 1999, 2000), that diminished with resolution of the lesions using thalidomide, pentoxyphylline, or prednisone. Cytokine inhibition was associated with resolution of the inflammatory response (Moraes, 2000). Lastly, Buno et al (1998) demonstrated increased mRNA for the cytokines INF-γ, TNF-α,and IL-2 in RAU and Natah et al (2000) demonstrated TNF-α immunoreactivity in association with macrophages, lymphocytes, mast cells, and vascular endothelial cells in biopsies of immuno-competent patients with RAU.

As in skin and GI mucosa, cells in the oral cavity participate in the regulation of host defenses during the process of inflammation. In addition to macrophages and T-cells, resident cells of the oral mucosa such as keratinocytes; epidermal cells, Kock, 1989, 1990); epithelial cells (Natah, 2000); and gingival fibroblasts (Meikle, 1989); produce TNF-α. In turn TNF-α acts on gingival fibroblasts to make IL-6, another pro-inflammatory cytokine (Takigawa, 1994), as well as the inflammatory mediator PGE_2 (Elias, 1987; Saito, 1990). Cytokines such as TNF-α and others exert their effects by binding to cellular receptors that in turn signal through second messengers. One group of second messengers is derived from hydrolysis of membrane phospholipids. Phospholipase A_2 cleaves its substrate to generate arachidonic acid, a precurser of eicosanoids, which act as inflammatory mediators. PGE_2 is one such eicosanoid produced by conversion of arachidonic acid via the cyclooxygenase pathway (reviewed by Gemmell, 2000) critical for coregulation of protease

production (He, 2002). TNF-α stimulates the production of PGE_2 (Dayer, 1985; Perkins, 1997) through the cyclooxygenase (COX) pathway and induces the degradation of collagen through activation of collagenases (Dayer, 1985; Meikle, 1989; Birkedal-Hansen, 1993). Interestingly, gingival fibroblasts stimulated with TNF-αcan participate in this process (Meikle, 1989). Hence, TNF-α together with these interleukins, appears to be involved in the initiation and progression of

connective tissue destruction.

3.2 ***Pain and RAU***

Pain is an inherent component of the definition of RAU. Evidence suggests that the immune response can mediate neural events (Morganti-Kossmann, 1992; Watkins, 1995), neuropeptides can regulate cytokine secretion (Levite, 2001), and cytokines can induce neuropathic pain via inflammatory insult (Fukuoka, 1994; Wagner, 1996; Woolf, 1997; Myers, 1999; Lindenlaub, 2000; Kidd, 2001). Pain in HIV/AIDS (Breitbart, 1998; Vogl, 1999), for example, may be due to aberrant cytokine expression contributing to neuropathogenesis (Irani, 1997), as cytokines regulate substance P expression in sympathetic neurons (Freidin, 1991). Animal studies of the role of TNF-α in pain suggest TNF-α directly induces nociceptive activity (Cunha, 1992; Nicol, 1997; Sorkin, 1997, Sommer, 1998a) and pain behavior (Sorkin, 2000; Homma, 2002). These reports are complemented by others demonstrating that anti-TNF treatment reduces pain behaviors in animal models (Sommer, 1998b, 1999, 2000; Lindenlaub, 2000; Ribeiro, 2000).

Convergent lines of evidence indicate that prostaglandins facilitate nociceptive activity. Sustained C fiber activity induces a rapid increase in the enzyme cyclooxygenase-2 (COX-2) via nitric oxide and a subsequent increase in prostaglandin synthesis. These actions facilitate neurotransmission and hyperalgesia (Sakai, 1998; Yaksh, 1999; Park, 2000). Zhang et al (1997) showed that by inhibition of COX-2, PGE_2 production was diminished, leading to attenuation of hyperalgesia after carrageenan challenge in the rat hind paw model of inflammatory hyperalgesia. In a clinical model of tissue injury, local tissue concentrations of prostanoids are temporally correlated with pain report, suggesting a functional relationship between their action and nociception (Dionne, 2002; Gordon, 2002; Khan, 2002). TNF-α promotes the expression of COX-2 leading to formation of PGE_2 and other inflammatory mediators that are important for nociception (Fournier, 1997; Perkins, 1997; Anthonsen, 2001; Chen, 2001), while thalidomide inhibits induction of COX-2 and prostaglandin synthesis *in vitro* (Fujita, 2001) and minimizes hyperalgesia *in vivo* (Sommer, 1997; Ribeiro, 2000).

3.3 ***Pathogenesis of RAU***

TNF-α and other Th1 cytokines have been implicated in many lesional diseases such as discoid (Toro, 2000) and systemic lupus erythematosus (Mongan 1997), lichen planus (Walsh, 1990; Sugermann, 1996), cutaneous lesions of leprosy (Barnes, 1992; Kaplan, 1993; Moraes, 2000; Sampaio, 1993; Sarno, 1991), and lesions associated with TRAPS (Toro, 2000). Although the etiopathology of RAU remains obscure, the chronic inflammatory nature of these lesions and their failure to resolve in an immuno-compromised host suggest that the pathogenesis of RAU is related, in part, to a cytokine-mediated inflammatory response or failure to resolve that response in the presence of immune dysregulation. This hypothesis is strengthened by clinical observations relating idiopathic recurrent mucosal lesions to several autoimmune syndromes, and by the efficacy of the

TNF antagonists and/or immunomodulator thalidomide for these and similar lesions of unknown etiology (Tamura, 1990; Bessis; 1992, Vogelsang, 1992, Revuz, 1990; Jacobson, 1997; Ordi-Ros, 2000).

3.4. ***Thalidomide***

Thalidomide was first synthesized in 1953 by the German company Chemie Grunenthal and marketed in1956 as a sedative-hypnotic drug under the trade name Contergan. With few apparent side effects and little toxicity in animal studies (Jung 1956; Kuhn and Van Maanen 1961; Fabro 1967; Locker 1971), thalidomide was subsequently marketed in a number of other countries. However, in 1961, McBride had noted an association between thalidomide use by pregnant women and congenital abnormalities. Lenz (1988) later estimated that while thalidomide was available, 5,000 to 6,000 cases of fetal deformities occurred, with 4,000 of these in Germany which were temporally-related to thalidomide sales. Thalidomide was withdrawn from the European markets in 1961, while it was pending approval by the FDA (Taussig, 1962; Kelsey, 1988; Fung 2001). Legal action was brought against Chemie Grunenthal which was settled in 1969 (Curran, 1971).

Concurrent with these events, Sheskin (1965) used thalidomide in a case series of five patients afflicted with erythema nodosum leprosum (ENL), a cutaneous manifestation of leprosy. His results were confirmed by Cazort and Song (1966). The success of thalidomide as a therapeutic agent in the treatment of this autoimmune inflammatory condition led other investigators to study thalidomide as a treatment for a number of other indications thought to have an autoimmune or inflammatory basis. Thalidomide was approved by the FDA on July 16, 1998 for the treatment of the cutaneous lesions associated with leprosy. In addition to controlled clinical trials for treatment of leprosy (Sampaio, 1993) and the mucosal lesions of RAU (Revuz, 1990; Jacobson, 1997, 2000, 2001), there are reports of the efficacy of PO thalidomide for other cutaneous lesions such as pyoderma gangrenosum (Munro, 1988; Hecker, 1998; Rustin, 1990), actinic prurigo (Londono, 1973; Khoo, 1999), sarcoidosis (Estines, 2001), and systemic and discoid lupus (Naafs, 1982; Warren, 1998; Ordi-Ros, 1999), as well as for oral mucosal lesions of Behcet's Disease (Jorizo, 1986; Eisenbud, 1987; Gardner-Medwin, 1994; Hamuryudan, 1998) and erosive lichen planus (Camisa, 2000). Thalidomide and other inhibitors of TNF-αhave also shown efficacy for the treatment of inflammatory bowel diseases (Targan, 1997; Ehprenpreis, 1999; Sandborn, 1999).

3.4.1. ***Pharmacology and Pharmacokinetic****s*

Thalidomide is an N-phthalyl-glutamic acid imide, a glutamic acid derivative. The chemical name is alpha-(N-phthalimido) glutarimide. The empirical formula is $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2. Thalidomide, or 1, 3-dioxo-2 (2', 6'-dioxopiperidine-3'–yl) isoindoline, is a compound that has two ring systems, the phthalimide moiety on the left and the glutarimide on the right. The 3' carbon atom, on the glutarimide ring is asymmetric. The compound may exist in either the optically active stereoisomers of dextrorotary (D +) or levorotary (L -) forms, or in an optically inactive DL (+) racemic mixture. The racemate is the form used clinically. Thalidomide hydrolyzes to 12 known metabolites. Although the activity of the metabolites is not well-characterized, from studies in animals it appears that the phthalimide portion of the molecule is active in immune modulation, as it—but not the glutarimide portion—inhibited lymphocyte responses to

phytohaemagglutinin (PHA) and concanavalin A (Con A) *in vitro*, as well as diminished signs and symptoms of GVHD (Vogelsang, 1988). The glutarimide part of the thalidomide molecule contains a chiral center. The enantiomers differ from racemic thalidomide in having higher solubility in water (Hague and Smith, 1988; Williams, 1965, 1968) and they undergo faster hydrolytic cleavage (Hague and Smith, 1988). Both enantimers are more toxic than the racemic mixture, with reported LD_{50} values in mice of 0.5 to 1.5 (for the S- form) and 0.4 to 0.7 g/kg (for the R+ form), respectively (Fabro 1967; Hague and Smith 1988), while racemic thalidomide is tolerated without toxicity in doses up to 5 g/kg in mice (Somers, 1960).

Though relatively non-lethal, racemic thalidomide and both enantiomers have been reported to produce malformations in animals (Fabro, 1967). Smith et al. (1965) reported teratogenic activity only for racemic thalidomide and the R(+) enantiomer; however, other investigators observed malformations only with S(-) thalidomide and its hydrolysis product, S(-) N-phthalyl glutamic acid, but not with their respective R(+) enantiomers (Blaschke, 1979; Ockenfels and Kohler, 1970; Ockenfels, 1976; Heger, 1988). Administration of a thalidomide analogue (EM 12) to marmosets showed that the enantiomers undergo spontaneous racemization in plasma (Schmahl, 1988, 1989). Only racemic and S(-) thalidomide prevent experimental GVHD (Field, 1966), although both enantiomers suppress leptromatous lesions (Sheskin, 1978).

Thalidomide is highly bound to plasma proteins, and is lipid soluble and hydrophobic, such that it has very limited solubility in water. As a result it can only be administered in very small doses intravenously in aqueous solution, but no such solutions have gained FDA acceptance for use in humans (Cosmetic Ingredient Review Expert Panel, 2000). Therefore, most of what is known about thalidomide pharmacokinetics is derived from enteral (PO) administration. The half-life of thalidomide in humans ranges from 5 to 8 hours, which varies slightly among healthy and immunocompromised patient populations. It is important to note that the thalidomide concentrations found to be effective *in vitro* (IC_{50} at 1-4 □g/mL) are similar to the plasma concentrations obtained in man after the administration of a single dose of 100-300 mg of thalidomide.

(i) *Absorption and Bioavailability*

Thalidomide is absorbed slowly after PO administration. The peak plasma concentration is reached in approximately four hours after a single 100 or 200 mg dose. Lack of a parenteral formulation has limited the determination of thalidomide's absolute bioavailability. The only published experiment concerning thalidomide bioavailability was conducted by Schumacher et al. (1968) using animal models. Area under the curve (AUC) for oral and IV administration was estimated at 93 and 67 percent. Comparing these values to estimates of V_d and CL from human studies show that they may be overestimates, as complete bioavailability was assumed. Intramuscular administration of thalidomide has also been unreliable; in guinea pigs thalidomide was found unabsorbed at intramuscular injection sites in excess of two days post-injection (Murdoch and Campbell, 1958).

(ii) *Distribution*

The plasma concentration versus time data after a single oral dose has been described as best fitting a one-compartment model (Chen, 1989; Piscatelli, 1997; Figg, 1999, Teo, 1999, 2001). Although Schumacher (1968) found that thalidomide obeyed two-compartment model kinetics after intravenous injection in rats and rabbits (5 mg/kg in dimethylsulfoxide-propylene glycol), other studies have not replicated this finding. In a number of species, including humans, the apparent volume of distribution of intact thalidomide exceeds the volume of total body water (Schumacher, 1970; Chen, 1989; Teo, 2001) and therefore thalidomide may be distributed extensively into tissue. However, animal studies do not indicate that thalidomide selectively localizes in any particular tissue (Faigle, 1962; Koransky and Ullberg 1964).

(iii) *Metabolism and Excretion*

In animal (Faigle 1962) and human studies the urinary excretion of thalidomide is negligible. Therefore, the major route of excretion of thalidomide is nonrenal (Faigle, 1962; Schumacher, 1965). This is probably due to the hydrolysis of thalidomide producing polar metabolites which are then renally excreted. Such hydrolysis products are most likely filtered by the glomeruli and are unable to be reabsorbed by the renal tubules resulting in excretion in the urine. A small portion of thalidomide and its hydrolysis products are excreted in the bile and there is some evidence for entero-hepatic circulation for such compounds (Schumacher, 1965, 1968).

(iv) *Biotransformation*

The rate of decrease in intact thalidomide concentrations *in vivo* in plasma is similar for a number of different species (Keller and Blake, 1971). The rate of elimination from plasma is comparable to that seen during spontaneous hydrolysis of thalidomide *in vitro* in aqueous buffers at physiological pH and at 37°C (Williams, 1968), indicating that thalidomide biotransformation is due to simple hydrolysis. In monkeys and rabbits, a small portion of thalidomide appears to be metabolized by an hepatic microsomal system (Schumacher, 1970).

3.4.2. Adverse Effects

The most significant adverse effects reported for thalidomide include teratogenicity, neurotoxicity, pruritis and rash, and somnolence.

(i) *Teratogenicity*

The teratogenic effect of thalidomide varies by species. In studies of the effect of thalidomide in pregnant animals of various species, it was concluded that mice, hamsters, rats, dogs, and cats were relatively resistant to the teratogenic effects of thalidomide, while rabbits and monkeys were very sensitive (Somers, 1962; Schumacher, 1970). Phocomelia is the predominant teratogenic effect manifested in humans, although the exact mechanism by which it occurs is unknown (DiPaole, 1969; Stephens, 1988; Neubert, 1996; Bauer, 1998). Humans appear to be particularly sensitive to the teratogenic effects of thalidomide. Fetal malformations most often occur when thalidomide is taken by pregnant human females between the 35^{th} and 50^{th} day after the last normal menstrual period

which is believed to correspond to the 21^{st} to 36^{th} day of post-fertilizational development for the embryo (Patten, 1953; Lenz and Knapp, 1962; Nowack, 1965; Pembrey, 1970).

(ii) *Neurotoxicity*

Peripheral neuropathy associated with long term thalidomide usage was first reported in 1960 in four patients receiving 100 mg of thalidomide daily for 18 to 24 months (Florence, 1960). In 1968 a group of investigators characterized the nature and duration of thalidomide-induced peripheral neuropathy (Fullerton and O'Sullivan, 1968). It was determined that 4 to 6 years after cessation of prolonged thalidomide therapy, approximately one half of patients who developed peripheral neuropathy exhibited no improvement in symptoms, one quarter of the patients had an improvement in symptoms but still manifested the condition, while the remaining patients recovered completely.

The severity of neurological changes detected in these patients correlated to the total amount of thalidomide administered, which indicates that peripheral neuropathy could be the result of direct activity by the drug (Garder-Medwin, 1994).

In a case series of six patients taking daily doses of thalidomide at 50 to 300 mg PO over a three year period, five of the six patients developed peripheral neuropathy. Abnormal electro-physiological results and symptoms of peripheral neuropathy were still present in one patient even a year after the thalidomide therapy was stopped (Clemmenson, 1984). In 1985, seven patients with prurigo nodularis and one patient with RAU were initially treated with 150 to 400 mg of PO thalidomide daily. This was later reduced to 25 to 100 mg per day and then in some cases to 50 mg every fifth day. Thalidomide therapy lasted over an eight-year period. All patients developed peripheral neuropathy predominantly of the lower extremities (Wulff, 1985). The authors of this study concurred with the conclusion of an earlier study (Gibbels, 1968) which stated that after administration of a 40 to 50 gram cumulative dose of thalidomide, neuropathy begins to develop in most patients.

Thalidomide polyneuritis is characterized by axonal degeneration without demyelination, a so-called "dying back process" resulting most frequently in peripheral neuropathy (Chapon, 1985; Fullerton and O' Sullivan, 1968; Krucke, 1971). The most prominent electrophysiological alteration is a decreased sensory nerve action potential (SNAP) amplitude (Lagueny, 1986), but decreased sensory and motor conduction velocities and alterations in latencies have also been observed (Clemmensen, 1984; Hess, 1986; Lagueny, 1986; Ludolph, 1982; Wulff, 1985). Electrophysiological abnormalities before the onset of subjective symptoms have been reported in several studies (Clemmensen, 1984; Hess, 1986; Lagueny, 1986; Ludolph, 1982).

An electrophysiologic study was performed on 13 patients with a variety of diagnoses receiving daily doses of thalidomide ranging from 50 to 200 mg PO over a two to six month period (Lagueny, 1986). With the exception of one patient with pyoderma gangrenosum, thalidomide resolved the lesions. However, subclinical neuropathic changes were detected in these patients with a reduction of sural and median nerve amplitude potential and an increase of somato-sensory evoked potential latency following nerve stimulation. In a study (Sheehan, 1986) where the efficacy of thalidomide was tested in ten patients with prurigo, neuropathic sequelae with clinical and electrophysiologic changes were found. These sequelae persisted in these patients even a year after cessation of thalidomide therapy. The conclusion was drawn that it is not possible to predict which patients will develop thalidomide-related neuropathy and if such neuropathy will be of a reversible nature. It has been suggested that the most prudent course of action would be to stop thalidomide therapy immediately if paraesthesia is detected, which would increase the possibility of reversing the neuropathy (Gunzler, 1992; Ochonisky, 1994; Khella, 2001).

Polyneuropathy symptoms worsen with prolonged drug treatment (Wulff, 1985; Bastuji-Garin *et al*, 2002; Chaudhry *et al*, 2002). In agreement with retrospective studies, some authors report delayed recovery after termination of thalidomide administration (Lagueny, 1986; Wulff, 1985), although others reported rapid improvement in a number of patients (Chapon, 1985; Clemmensen 1984). Patients with pre-existing neuropathies are at higher risk for the development of thalidomide polyneuritis (Gutierrez-Rodriguez, 1988; Hoyer, 1983; Bastuji-Garin *et al*, 2002; Chaudhry *et al*, 2002). Conversely, neuritis present during ENL episodes are improved by thalidomide treatment purportedly due to suppression of the inflammatory process (Sheskin, 1969, 1979; Boddingius, 1977). Although thalidomide neuropathy was not observed after repeated ENL episodes treated with

thalidomide (Sheskin and Yarr, 1979), it may be difficult to differentiate thalidomide-induced changes from the neuropathological changes caused by the underlying disease.

(iii) Pruritis and Rash

Skin rash has been widely reported with thalidomide use (Burley, 1959; Waters, 1971; Calnan and Meara, 1977; Hamza, 1986; Eisenbud, 1987; Salafia and Kharkar, 1988). Treatment with thalidomide was halted due to persistent rash in three of eight HIV patients being treated for RAU in an unblinded case series (Williams, 1991). In an open-label study of 56 HIV+ patients treated for cachexia, cutaneous and febrile reaction was the most frequently observed toxicity, occurring in 36 percent of patients, and accounting for the majority of the drop-out rate (Haslett, 1997).

(iv) *Somnolence*

The most frequently observed effect is related to the sedative action of thalidomide. Thalidomide acts directly on the central nervous system, as evidenced by electroencephalographic changes in guinea pigs, rabbits, and humans (Hague, 1969). In mice, this effect was characterized by a decrease in spontaneous activity, relaxation of skeletal muscle, and sleep. During thalidomide-induced sleep, the righting reflex remained intact, there were no effects on motor coordination, and the animals could be readily awakened (Somers, 1960). Even at the highest doses of thalidomide (up to 5 g/kg in mice), deep narcosis, anesthesia, respiratory center depression, or death do not occur (Merrell, 1965). In humans, doses as high as 900 to 1200 mg PO per day have been administered, resulting in sedation, but not respiratory depression or death (Figg, 1999, 2001).

(v) *Drug Interactions*

Drug interactions with thalidomide have not been systematically studied in humans. In animal studies, thalidomide enhances the activity of barbiturates, alcohol, chlorpromazine, and reserpine, and its sedative action is antagonized by methylamphetamine and methylphenidate (Sommers, 1960). The possibility of thalidomide causing adverse effects in patients with HIV-related encephalopathy cannot be excluded, particularly if patients simultaneously receive other drugs that act on the CNS. Thalidomide was found to antagonize the action of histamine, serotonin, acetylcholine, and

prostaglandins in organ bath experiments (Hastings, 1976), but had no influence on the uterine reaction to oxytocin, vasopressin and histamine (Locker, 1971).

Other serious adverse experiences reported in humans using thalidomide are described in Celgene's report of adverse event surveillance (Clark, 2001), as well as the package insert for Thalomid® (Celgene, city, state). Notably, neutropenia (Barosi, 2001) thrombosis (Flageul, 2000, Osman, 2001; Pouaha, 2001; Bennett *et al*, 2002; Desai *et al*, 2002), myeloproliferative reactions (Barosi, 2000; Tefferi, 2000), and fatal reactions such as toxic epidermal necrolysis (Rajkumar, 2000). Stevens-Johnson Syndrome and sepsis have been reported since thalidomide use has increased. A report by Teo, et al (2002) confirms the 1997 report of Jacobson, *et al* of increases in viral load with thalidomide use in HIV infected patients. Importantly, these adverse effects are treatment limiting, as reflected by a high withdrawal rate from several clinical trials. For example, in a study of standard dose thalidomide for myelofibrosis, treatment was discontinued in 90.5 percent of subjects secondary to adverse effects, primarily somnolence (Barosi, 2001). The ACTG trial for RAU in HIV seropositive patients was characterized by almost a 50 percent drop-out rate

(Jacobson, 1997, 2001). In an open-label evaluation of thalidomide for cachexia, the drop-out rate was 43 percent, mainly due to rash and/or fever (Haslett, 1997).

3.5 Thalidomide and RAU

Although the anti-inflammatory, analgesic, and anti-neoplastic properties of thalidomide were first described in the 1960's (Miller, 1960), it has been only rediscovered recently for those applications. As a result, the mechanisms of action are still being elucidated. *In vitro* studies indicate that thalidomide is capable of inhibiting TNF-α production (Turk, 1996) by accelerating the degradation of mRNA encoding the protein and thus inhibiting the release of TNF-α from activated mononuclear blood cells (Zwingenberger, 1996; Tavares, 1997). However, a number of other mechanisms have also been proposed. *In vivo* data demonstrate anti-angiogenic activity, leading to current testing of thalidomide for the treatment of malignancies (Figg, 1999, 2001; Rajkumar, 2000; Myers, 2001). Anti-angiogenic properties may account for its effect on developing limb buds, as may its arene oxide metabolites, implicated as mutagens, cytotoxins, and teratogens. Another proposed mechanism of action is inhibition of integrin activity that relates to inflammatory cell recruitment into tissues (Neubert, 1996). Thalidomide has been shown to inhibit neutrophil migration (Carneiro-Filho, 2001) and causes neutropenia (Barosi, 2001). Similar to its actions on TNF-α, thalidomide has also been shown to inhibit IL-12 production (Gazzinelli, 1995; Moller, 1997), but also to increase it (Haslett, 1999).

Viewed together, these basic and clinical research findings suggest a net anti-inflammatory effect of thalidomide via suppression of inflammatory cell trafficking leading to a reduction of pro-inflammatory cytokines and other inflammatory mediators. However, Jacobson (1997) reported unexpected increases in the plasma concentration of TNF-α and soluble TNF receptors in HIV seropositive patients treated with PO thalidomide for RAU. Moreover, HIV viral load increased significantly in the group receiving PO thalidomide as compared to the group receiving placebo. Although the mechanism for the increase in viral replication was not assessed in that study, thalidomide has been shown to enhance T-cell proliferation and IL-2 production (Shannon, 1997). A pro-inflammatory action of thalidomide has been reinforced by recent reports of increased plasma pro-inflammatory cytokine concentrations in patients being treated with thalidomide. TNF-α and

IL-12 were elevated in scleroderma patients (Oliver, 2000) and in Toxic Epidermal Necrolysis (TEN) patients being treated with thalidomide (Wolkenstein, 1998). In both of these studies elevation of these plasma cytokine concentrations were accompanied by life-threatening sepsis.

The differential responses of cytokine effect and modulation are environmentally dependent, i.e., based on co-regulatory molecules and events. This may explain why in some conditions thalidomide up-regulates TNF-α and in others decreases its production. This, too, strengthens our rationale for use of a topical formulation of thalidomide. The apparent contradiction as to whether thalidomide inhibits or enhances TNF-□ in *in vitro, ex vivo,* and in clinical studies may have several explanations, including: 1) methodologic differences in preparation affecting how thalidomide is dissolved, whether it is completely dissolved, and what effects the solution has on cells; 2) differences in concentrations used in *in vitro* and *ex vivo* experiments, in that differential effects may be concentration-related; 3) related to cell types and what cytokines are present; 4) related to type of stimulation used; and 5) lack of comparability between *in vivo* / *ex vivo* studies and clinical conditions. In our preliminary studies (through protocol 96-D-0095), we have found increased local levels of TNF-α(in saliva and ulcer exudate) associated with higher plasma concentrations of TNF-

αin subjects with ulcers compared to those whose ulcers have healed. It is important to confirm these observations in a larger number of subjects to determine whether topical thalidomide may be safer than delivery by the oral route. Further, confirmation of our preliminary findings of TNF-α associated with ulcer healing will offer important information about the role of this cytokine in the pathogenesis of RAU. Results from the dose-finding study are summarized next.

3.6 Dose Finding Study

The dose-finding study was a prospective, interventional study with a parallel groups, double-blind design. Pain was the primary motivation for participating in the study. Pain intensity at baseline was similar between groups and rated as moderate on the category scale, equating with > 30 mm on the VAS (100 mm line). Subjects in the 20 mg drug group had marked reduction in pain from baseline to the last visit (P = 0.025). Subjects who did not heal continued to report pain and this was the principle reason for discontinuing use of the topical study drug. A dose response pattern was also observed for subjects electing to discontinue topical in favor of open label thalidomide. Probability of ulcer healing was highest for the 20 mg dose (87.5 percent), and a positive trend for dose response was observed. The mean time to ulcer healing was 17 days for the 20 mg group versus 23 days for the placebo group and there were more unhealed ulcers (60 percent) in the placebo group compared to the other groups. For those not healed on topical, healing after using thalidomide capsules at 200 mg per day was similar to previously published results. In order to estimate the effect of dose on healing, adjusting for contribution of other variables (use of combination anti-retroviral therapy and biopsy), a logistic regression model was fit to the data. Dose was the only significant contributor to the model. Addition of biopsy and combination anti-retroviral therapy to the model did not significantly change the estimated coefficient for healing.

For comparison of topical mucosal absorption and tolerability, healthy volunteers served as their own controls in three random, double-blind allocations of 0, 5, or 20 mg of topical thalidomide in an allocation scheme counterbalanced for order effect. Although the amount of drug in the mucosal tissue was not quantified, the amount of drug measured in plasma was taken as a measure of approximate absorption, as bioavailability is the fraction of the administered drug dose that reaches the peripheral circulation unchanged (Sitar, 2000). The 20 mg dose was detectable at one time point (3 hr) in healthy volunteers with intact mucosa, but all other doses of topical thalidomide were undetectable or below the limit of quantification. In HIV+ subjects with ulcers, the placebo, 5, and 10 mg doses were either not detectable or below the level of quantification, while the 20 mg dose was detectable at 5 min post-application (0.15 $\pm$ 0.23 □g/mL), highest at 1 hr post-application (averaging 0.2 □g/mL), and decreased, but remained detectable at a little over 0.1 □g/mL over the course of the remaining observation period of four hours. The length of the observation period was insufficient to determine when thalidomide would again diminish to an undetectable level in the 20 mg group.

Adverse events were similarly distributed between all doses and placebo in HIV+ subjects with oral lesions as well as in healthy volunteers with intact mucosa, and no subjects discontinued the study medication secondary to adverse effects, nor were any dose reductions necessary. No neurologic changes were noted by patient report, neurologic examination, or electromyography. Neither plasma HIV-1 RNA nor T-cell counts varied significantly from baseline to the end of the study in either HIV+ group. The results of the dose-finding study were submitted to the FDA for

review according to reporting requirements.

4.0 Experimental Design and Methods

This study will employ a prospective intervention using a parallel groups, double-blind design. Treatments will be compounded, tested for stability, and dispensed by the Pharmaceutical Development Service (PDS) at NIH to a Data Coordinating Center for randomization and allocation to participating clinical sites. Study participants will be informed regarding the nature of the study and requirements for participation, as well as potential risks and benefits. In accordance with the NICDR Institutional Review Board and the bylaws of the NIH Clinical Center, written informed consent will be obtained from all study participants, and they will be free to withdraw from the study at any time. Subjects will undergo treatment at selected clinical sites across the country.

4.1 Selection Criteria

4.1.1 Inclusion criteria

Persons with HIV infection or acquired immunodeficiency of at least 18 years of age with one or more chronic, painful intraoral lesions are eligible for screening. Lesion chronicity is defined as at least two weeks' duration without resolution using standard available treatments. Subjects must be under the care of a primary physician for management of HIV disease, and must have HIV/AIDS diagnosis confirmed by the primary physician. Patients' HIV treatment regimen will not be altered during the course of the study. Lesion eligibility criteria will be based on diagnostic criteria as described by the USA Oral AIDS Collaborative Group workshop (Greenspan 1992): existing lesions consistent with RAU refractory to standard therapies, and absence of a positive diagnosis of HSV and candidiasis. Patients with lesions meeting these stated criteria will be enrolled. If the lesion is subsequently found to be herpetic or fungal after the culture and biopsy results, the patient will be removed from the study, treated accordingly, and re-evaluated if the ulcer remains. RAU are characterized as chronic or non-healing in HIV+ patients. This study design uses the No Progress disease model (Holford, 2001), which assumes that baseline remains constant without intervention. Therefore, in this study, healing should not occur without intervention.

4.1.2 Exclusion criteria

Patients will be excluded from participation if taking any concurrent treatment for mucosal lesions (including topical or systemic steroids, viscous lidocaine, topical or systemic anti-fungals, or mouthwashes), concurrent thalidomide therapy, chemotherapy or radiation therapy for neoplasm, concurrent acute therapy for opportunistic infection, concurrent use of sedatives (such as CNS depressants or alcohol use), history of allergy to thalidomide, and females of childbearing potential. Women of childbearing potential, pregnant or lactating females will be excluded. Patients unwilling to adhere to precautions as described in Section 4.2 will be excluded.

4.2 Procedures

Eligible subjects will be selected via phone screening to participate in a screening evaluation consisting of completion of a self-reported health assessment by health history questionnaire and undergoing a brief physical, including oral and head and neck evaluation. The oral examination will determine the location and size of the lesion(s), as well as confirm the lesions meet the diagnostic criteria for RAU (Section 4.1.1). The differential diagnosis of ulcers in the oral cavity includes those

caused by HSV and RAU. Accurate diagnosis between these two entities is an important distinction, as herpetic ulcers are readily treatable while aphthous ulcers are recalcitrant to treatment. Previous studies have demonstrated that HSV can be reliably diagnosed by culture, and our preliminary study demonstrated that the concordance of diagnosis for HSV by biopsy versus culture supports use of culture alone to rule out HSV. Subjects who meet eligibility criteria and elect to participate will furnish demographic data and complete a baseline pain evaluation using a four-point category scale and 100 mm visual analog scale (VAS) for pain sensory intensity. Participants will also be provided with a diary to record pain, analgesic intake, and side effects at baseline and on a weekly basis over the course of the study.

Oral health assessment of hard and soft tissues will be performed using the Decayed-Missing-Filled-Surfaces (DMFT) index and the modified Gingival Index for periodontal status, using methodology described by the National Institute of Dental Research: Diagnostic Criteria and Procedures (U.S. Dept HHS 1991). Oral lesions will be photographed using an intraoral camera (Yashica Dental Eye® with macrolens, Kyocera Electronics, Inc., Somerset, NJ) and size referenced with a calibrated dental probe (millimeter rule, University of North Carolina No. 15 probe; Hu-Friedy, Chicago IL) placed in the field of vision. The dental probe will be used to make two measurements at perpendicular angles of the lesion's width and length and the product will be calculated as surface area (mm^2). When there is more than one ulcer, the total surface area will be recorded as the sum of the surface areas, up to a maximum of three of the largest ulcers. This is the same methodology used by the AIDS Clinical Trial Group (ACTG 251) to study the effect of PO thalidomide for RAU (Jacobson, 1997, 2000, 2001). In addition, image analysis of the photographed lesions will be performed by a blinded observer.

After questionnaires, examination, and photographic documentation, the following specimens will be obtained in the order listed: blood samples, whole unstimulated saliva, ulcerative exudate, and culture for HSV and candidiasis. The site investigator will place the first dose. Subjects will be instructed on application of the topical ointment, oral hygiene and lesion care, and dosing regimen such that all other doses will be placed by the subject. Subjects will remain in the clinic for a five hour observation period following placement of the first dose. They will complete pain and side effects questionnaires and maintain an analgesic diary daily between study visits. Subjects will return weekly to reassess pain, lesion size, and adverse effects until healing occurrs or four weeks pass without lesion resolution.

Subjects will be contacted by telephone every three days and asked to return to the clinic at weekly intervals. Compliance will be assessed during phone calls, and at follow-up visits by diary checks and monitoring of their ability to apply the topical ointment. Drug regimen and precautions will be reinforced at these visits. Subjects may withdraw from the study at any time. Subjects who do not heal in four weeks can elect to use PO thalidomide and will be monitored by the same criteria and duration. Analgesic usage will be standardized to acetaminophen, and evaluated through diary recordings and pill counts.

4.2 Toxicity monitoring and management

Adverse effects will be evaluated by patient self-report and examination. The most common side effects are sedation, rash, the development of peripheral neuropathy, and teratogenicity. Patients have 24 hour emergency access to the investigators and will be encouraged to report any adverse

effects experienced by diary and by phone. Patients will contact the clinical site investigator if rash or itch is experienced between visits. Subjects experiencing rash or confirmed allergic reaction will be discontinued from participation in the study. Patients will also be encouraged to contact the investigator if drowsiness is experienced between visits. Subjects experiencing sedative effects will be counseled individually concerning continuation in the study. Site investigators will report adverse events to the Data Coordinating Center (DCC) on a schedule to be determined by the Data Safety Monitoring Board (DSMB). The DSMB will be established according to the guidelines for the establishment and operation of NIH DSMBs, found at http://www.nidr.nih.gov/clinicaltrials/data_safety_guidelines.asp after establishment of the DCC.

All adverse events will be reported at each annual continuing review. Unexpected serious adverse events that will be reported according to the NIH 7/15 day policy include allergic reaction or pregnancy. We will not report the types of anticipated adverse events as specified in the protocol, except at the annual review. Similarly, we will not report the adverse events that are unlikely to be related to the study, such as hospitalization for trauma, pre-existing chronic conditions and their sequelae (ie, consequences of HIV infection and manifestation of AIDS), or for elective reasons.

To minimize the potential for teratogenicity, females of childbearing potential will not be permitted to participate. Women surgically sterilized by means of hysterectomy or tubal ligation will be allowed to participate given negative urine pregnancy tests at specified time points. Women will be tested for pregnancy via urine pregnancy tests at baseline (initial physical exam), every two weeks during study participation, and four weeks following conclusion of the study. Due to age variation surrounding menarche, ovulation after menopause, and the possibility of amenorrhea occurring with

severe illness, women reporting menopause, but not surgical sterilization, will not be permitted to participate. Patients unwilling to adhere to the precautions recommended by the FDA will not be allowed to participate. Specifically these precautions for female participants include abstaining from reproductive sexual intercourse or use of two highly effective birth control methods at the same time for at least a month prior to receiving thalidomide and continuing regularly thereafter until one month after the last dose. For male participants who are not surgically sterilized, precautions include abstainance from reproductive sexual intercourse, or use of a condom while receiving thalidomide and continuing thereafter until one month after the last dose. The following table summarizes the toxicity management plan.

Sign/Symptom	Criteria	Action
Somnolence	Persisting 72 hours	Half the administered dose.
Somnolence or other CNS changes per patient report	Persisting 72 hours beyond dose reduction	Discontinue from study participation.
Rash	Grade I - II	Withold study medication and evaluate. If rash returns when medication is resumed, discontinue from study participation.
	Grade III - IV verified through dermatology consult	Discontinue from study participation.

Peripheral Neuropathy	Grade II neuropathy verified through neurology consult	Discontinue study medication until improvement. If no improvement or a return to Grade II, discontinue from study participation.
Neutropenia	Absolute polymorphonuclear cell count < 1500/mm^3	Discontinue study participation.
Thrombocytopenia	Platelet count < 100,000/mm^3	Discontinue study participation.
Viral Burden	Increase > 0.5 log from baseline as confirmed by two measurements by bDNA	Withold study medication. If returns to 0.3 log increase above baseline, reinstitute drug at half the dose; if remains elevated, discontinue study participation.
Hepatotoxicity	AST, ALT, alkaline phosphatase, total protein, albumin, amylase, or bilirubin >= twice the normal upper limit of the normal range	Discontinue study participation.
Renal Toxicity	Serum creatnine or blood urea nitrogen >= twice the upper limit of the normal range	Discontinue study participation.
Other Toxicities	As presented by patient. Includes monitoring of CBC and differential, CD4 & CD8, hematocrit, coagulation panel, and electrolytes within twice the normal upper and lower limits of normal ranges.	Discontinue study medication until improvement. If no improvement or a return of the sign or symptom, discontinue from study participation.

4.3 Hematologic sampling (selected clinical sites)

Blood samples (7 mL) will be collected as delineated below, centrifuged, and plasma decanted and stored at -70 ^{o}C for later measurement of blood thalidomide levels.

#	Time of Collection
1	Baseline
2	5 min after first dose
3	30 minutes after first dose
4	1 hour after first dose
5	2 hours after first dose
6	3 hours after first dose
7	4 hours after first dose
8	5 hours after first dose

Blood drawn for monitoring of viral load will be partitioned for evaluation of TNF-α plasma concentration.

4.4 Follow-up observations

Subjects will return weekly for evaluation until the end of study. Female subjects will be asked

to return to the clinic 4 weeks following their last dose of drug to undergo a pregnancy urine test. Subjects reporting adverse effects up to 4 weeks following their last dose will be further evaluated.

5.0 Hazards and Discomforts

The most common side effects associated with chronic thalidomide administration--drowsiness, rash, and peripheral neuropathy--will be quantified to permit evaluation of the relationship between route of administration and adverse events. Topical administration may decrease the incidence of these side effects by producing lower blood levels of thalidomide than PO administration. Data from our preliminary study showed adverse events similarly distributed between all doses and placebo in HIV+ subjects with oral lesions as well as in healthy volunteers with intact mucosa. No subjects discontinued the study medication secondary to adverse effects, nor were any dose reductions necessary. No neurologic changes were noted by patient report, neurologic examination, or electromyography. Further, neither plasma HIV-1 RNA nor T-cell counts varied significantly from baseline to the end of the study in either HIV+ group. However, patients participating in this study will be exposed to the risks associated with the use of the drug thalidomide as described in section 3.4.2 and 4.2. Discomfort may result from swabbing of the oral lesion to obtain samples and cultures. Venipuncture may cause discomfort or a hematoma. Inconvenience associated with participation in this study is the number of return visits to the clinic for follow-up (one time per week), and for women, return at 4 weeks post-study for urine pregnancy test.

6.0 Benefits

Subjects in the active treatment group may receive therapeutic benefit of the drug, which is not currently available. Subjects may in addition experience fewer side effects using topical thalidomide than if they used PO thalidomide. Positive results from the study may develop into a new treatment regime which may have a far-reaching impact for improving the oral health and quality of life of these individuals.

7.0 Significance

Side effects are common in HIV/AIDS patients receiving drug therapies. Given the severity of the pain and dysphagia associated with oral lesions in HIV/AIDS patients and their recurrence due to the chronic, progressive nature of the disease, PO thalidomide continues to be used for oral lesions refractory to other treatments. Development of alternatives to PO administration of thalidomide may lower the incidence and severity of thalidomide toxicity and produce improved healing of the lesions, as well as contribute to enhanced quality of life in this patient population. Given the growing numbers of patients with HIV infection which will eventually result in the development of oral lesions, and the absence of any other effective treatment for these painful and debilitating ulcerations, the need exists to develop treatment strategies to limit the toxicity associated with the administration of thalidomide to this patient population. Lastly, elucidation of the role of TNF-α in the pathogenesis of these lesions may provide a rational target for alternative treatments.

8.0 Sample Size Estimate

The primary hypothesis to be tested pertains to healing and the second to pain relief. Based on data from the dose-finding study, we believe that there will be a robust difference in healing between placebo and 20 mg topical ointment. From our preliminary data, there was a trend for dose response in pain relief. Since we wish to also include pain relief as a secondary outcome measure, we have based the sample size estimate on the difference in pain report at the end of the study as measured by a standard 100 mm visual analog scale between the placebo and 20 mg topical thalidomide groups. Data from the dose-finding study were entered into the sample size program Power Analysis and Sample Size (PASS) by NCSS Statistical Software using a variety of alpha and beta values in order to visualize the potential sample size space. From the data, an alpha level of 5 percent with 80 percent power will be more than sufficient for inference. Hence, sufficient power can be achieved when n = 68.

n	□	□
92	0.05	0.10
68	0.05	0.20
102	0.01	0.20

The preliminary study using topical thalidomide had a 10 percent drop-out rate and the literature reports between a 10-30 percent drop out rate; albeit for use of PO thalidomide where somnolence is the main reason for study withdrawal. Hence, an approximate 15 percent attrition rate is added, rendering approximately 160 subjects as the sample size (i.e. 80 patients are to be assigned to each of the two treatment groups). The total number of subjects is projected for 68 x 2 groups = 136 subjects, before adjusting for attrition.

9.0 Study Analysis

The DCC will design and implement a data entry and edit system to insure completeness, quality and uniformity of all data. Pain, lesion size, and adverse effects will be assessed at baseline and over time, with the primary analysis using baseline and end of study variables. Data will be analyzed using Student's T-test for continuous measures and chi-square for categorical and frequency data. The primary outcomes of proportion healed, and time to healing will be assessed by the Kaplan Meier method of survival analysis. Incidence of adverse effects between groups will be compared by Yate's corrected chi square analysis. DMFS and periodontal diagnosis will be examined for any relationship between oral health status and lesion size and duration.

According to an approved data management plan, forthcoming following establishment of the DCC, analyses of data requested by the Data and Safety Monitoring Board and/or the Principal Investigator (PI) will occur as follows:

1. Prepare detailed analyses of accumulated data for the DSMB to monitor the study for adverse and beneficial treatment effects at intervals determined by that committee and the PI. These analyses shall assess positive and negative aspects of the effectiveness of any treatments under study.

2. In collaboration with the DSMB, the DCC and PI shall review the database for possible analyses to aid in the monitoring of or improving the quality of data.

3. Develop new or modified methods of analyses that meet the specific needs of any the study.

The molecular endpoints of TNF-α □□□ plasma blood levels of thalidomide will be examined, but not subjected to statistical testing.

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