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**PROTOCOL
AND
PROTOCOL AMENDMENTS**

CLINICAL TRIAL PROTOCOL

A Double-Blind, Randomized Phase II/III Study of GL701 in Female Patients with Mild to Moderate Systemic Lupus Erythematosus

Protocol No.: GL94-01

Date: March 14, 1994

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I have received and read the Investigational Drug Brochure for GL701 dated 12/93, the protocol dated 3/14/94, and the Statement of Investigator Obligations. I agree to undertake the study as defined therein. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved by Genelabs Technologies, Inc. and the Institutional Review Board. Failure to adhere to those stipulations may constitute a breach of federal regulations and may result in termination of the study.

Investigator
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PROPRIETARY STATEMENT

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1. BACKGROUND AND RATIONALE

1.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (*SLE*) is a chronic, autoimmune, inflammatory disease that may affect the skin and joints, as well as internal organs, such as the heart, lungs, kidneys, spleen, nervous system and serous membranes lining the lungs, heart and abdominal cavity.

Approximately 65% of patients develop *SLE* between 16 and 55 years of age, and it is 8 to 10 times more common in women than in men. The overall prevalence of *SLE* ranges from 40 to 50 per 100,000 individuals in the U.S. and it appears to be more common in black females than white females (Lawrence et al, 1989).

Although the etiology of lupus is unknown, it is thought that hormonal, environmental and genetic factors may all be implicated.

Hormonal influences seem to play a key role in disease development and progression. Beyond the increased incidence in women, several studies have noted alterations in estrogen and androgen metabolism occur in patients with lupus. Decreased levels of androgens (androstenedione, DHEA, DHEA sulfate and testosterone) have been observed in female lupus patients, especially in those with active disease (Lahita et al, 1987; Jungers et al, 1983). Environmental factors appear to contribute to the development of *SLE*. While *SLE* is most often idiopathic, some factors such as drugs (procainamide, hydralazine), dietary factors (L-canavalin) and exposure to ultraviolet (UV) light have been shown to induce lupus or a lupus-like syndrome or exacerbate underlying disease. Genetic factors may also play a role in the development of *SLE*. Relatives of persons with *SLE* have a higher prevalence of lupus than the general population as well as a higher rate of immunologic abnormalities.

Patients with *SLE* produce autoantibodies, notably antinuclear antibodies (*ANA*), directed against double-stranded DNA (*anti ds DNA Abs*) or ribonucleoprotein (*anti Sm or anti RNP Abs*). Patients with *SLE* also produce antibodies to phospholipids, erythrocytes, granulocytes, lymphocytes and macrophages.

The formation of antigen-antibody complexes (immune complexes) can lead to complement binding and subsequent depletion (decreased C3, decreased C4 and/or decreased CH50), a hallmark of the disease. Complement binding leads to release of chemotactic factors, thereby attracting phagocytic cells causing further tissue injury. In mesangial and proliferative glomerulonephritis, for example, immune complexes may be deposited in the glomerular basement membrane.

Systemic lupus may include periods of remission and flares. The American College of Rheumatology has determined that the diagnosis of *SLE* should be made if 4 or more of the manifestations as listed in Appendix 11.1 were present, either serially or simultaneously during any interval of observation. (Tan et al, 1982)

Systemic manifestations common in lupus patients include fatigue, fever, arthritis, arthralgia and weight loss, and skin rash. Virtually every organ system may be involved in lupus. Among the most important are:

Renal system	Mesangial, focal proliferative, diffuse proliferative and membranous glomerulonephritis
Central nervous system	Psychosis, seizures, cerebrovascular accident and neuropathy
Hematologic	Thrombocytopenic purpura, hemolytic anemia and severe granulocytopenia
Cardiovascular	Myocarditis, pericarditis and marantic endocarditis
Pulmonary	Pulmonary hypertension, pneumonia and interstitial pneumonitis

The differential diagnosis of SLE includes rheumatoid arthritis, other connective tissue or autoimmune diseases (mixed connective tissue disease (*MCTD*), systemic sclerosis), lymphoma, leukemia, subacute bacterial endocarditis, and infections including sepsis.

Patients with mild to moderate symptoms are usually managed with administration of analgesics, nonsteroidal anti-inflammatory drugs (*NSAIDs*) and sunscreens. However, *NSAIDs* may reduce glomerular filtration rates and renal blood flow, cause gastrointestinal bleeding and can be associated with hepatotoxicity.

If symptoms are not well controlled by these therapies, the patient's treatment may be augmented by the addition of an antimalarial drug, such as hydroxychloroquine (*Plaquenil*), although chloroquine and quinacrine are used less frequently. Toxicities with these agents include retinopathy with hydroxychloroquine and chloroquine, aplastic anemia with quinacrine, skin pigmentation changes, as well as development of peripheral neuropathy and myopathy with hydroxychloroquine only.

For patients who do not respond to conservative therapy, glucocorticoids in relatively low doses (i.e., prednisone \leq 35 mg/day) are prescribed for their anti-inflammatory and immunosuppressive actions. Concerns arise in managing the severe toxicities associated with chronic administration of glucocorticoids, including infection, hyperglycemia, hypertension, osteoporosis, ischemic necrosis of bone, and cataracts.

Thus, the goal of glucocorticoid therapy in SLE is to use the lowest effective dose. However, during glucocorticoid taper, patients may experience symptoms of glucocorticoid withdrawal (fever, joint pain, malaise, frank arthritis) and the underlying disease may flare.

If therapy has not been effective or the patient has serious or life-threatening manifestations of lupus, then more aggressive management is warranted. Immunosuppressive agents such as azathioprine (*Imuran*) and cyclophosphamide (*Cytoxan*) are used for patients with life-threatening or major organ system involvement. Toxicities associated with administration of azathioprine include leukopenia, and thrombocytopenia. Cyclophosphamide can result in urinary bladder toxicity, sterility, teratogenic effects, mutations, and cancer.

High dose glucocorticoid therapy (e.g., intravenous methylprednisolone of 1 gram/day and daily doses of 40-60 mg prednisone) is associated with aseptic necrosis, osteoporosis and psychosis, in addition to the toxicities previously described.

Disease progression is highly variable and is difficult to predict from one individual to another. It is generally agreed that renal disease and pulmonary hypertension carry the worst prognosis. During periods of disease activity, it is important to treat early and aggressively to maintain internal organ function. Deaths occur primarily from severe systemic infections and renal insufficiency. Patients with longstanding SLE may succumb to atherosclerotic cardiovascular disease, believed in part to be due to chronic use of corticosteroids.

Life expectancy has improved considerably in the last several years. From 1954 to 1983, 1 year survival for lupus patients increased from 78% to 95%; for 4 year survival from 52% to 88%; and for 10 year survival in 1983 was expected to be 76% (Hahn, 1993).

1.2 DHEA

Dehydroepiandrosterone (*DHEA*) is a naturally occurring steroid produced by the adrenal glands, testes and brain. Its metabolite, DHEA sulfate (*DHEA-S*), is the most abundant circulating adrenal steroid in the human and is subsequently converted into testosterone and estrogens. Secretion of DHEA is synchronous with cortisol, with a diurnal variation, while DHEA-S levels show little variation during the day. Blood levels of DHEA-S are high in the fetus and decline to near zero after birth, increasing again prior to puberty, and peaking at age 20 to 25. Unlike cortisol, levels of DHEA-S decline progressively thereafter to approximately 5 to 10% of peak values at age 60 to 70 (Orentreich et al, 1984). With aging, the circadian rhythm of secretion and stimulation following ACTH administration are lost (Parker, 1991).

In addition to age, genetic factors as well as sex account for a wide variation in circulating levels of DHEA and DHEA-S (Rotter et al, 1985). Levels are significantly lower in women (Carlstrom et al, 1988). This may be due in part to a functional shift in 17, 20 desmolase enzyme activity in the adrenals which is upregulated during adrenarche and downregulated after menopause (Schiebinger et al, 1981; Liu et al, 1990).

The inactive metabolite, DHEA-S, is converted by peripheral tissues containing DHEA sulfatases, including lymphocytes and macrophages, to DHEA. DHEA is subsequently metabolized to androstenedione as well as potent androgens: testosterone and dihydrotestosterone (*DHT*) and estrogens: estrone (*E1*) and estradiol (*E2*). Adipose tissue may serve as a substantial reservoir for adrenal androgens. The aromatization of DHEA in peripheral tissue is thought to account for the majority of estrogen biosynthesis in postmenopausal women (Grodin et al, 1973).

Although DHEA is the major secretory product of the adrenal gland, its biologic function in the human, other than as a precursor of sex steroids, has not been ascertained. Two epidemiologic studies have linked declines in DHEA levels with the development of breast cancer in women (Bulbrook et al, 1971) and cardiovascular disease in men (Barrett-Conner et al, 1986), although a subsequent study failed to confirm the link between breast cancer and low serum levels of DHEA (Barrett-Conner et al, 1990). Other studies have linked age-related decreases in DHEA and DHEA-S levels to decreased bone mineral density in postmenopausal women (Wild et al, 1987; Taelman et al, 1989; Spector et al, 1991), particularly in those with rheumatoid arthritis who have received glucocorticoid therapy (Sambrook et al, 1988; Dias et al, 1989; Hall et al, 1993; Deighton et al, 1992). Again, epidemiologic studies have failed to confirm the association between low DHEA levels and osteoporosis (Nordin et al, 1985; Barrett-Conner et al, 1993). Similarly, low serum levels of DHEA have been related to Alzheimer's disease (Sunderland et al, 1989) and to the loss of immunocompetence with aging (Thoman and Weigle, 1989; Daynes et al, 1992).

Nafziger et al (1991) reviewed the relationship of DHEA and DHEA-S to cardiovascular disease. Several observations suggest a direct relationship in men, although in women the data are not so clear:

- Serum DHEA levels are inversely associated with cardiovascular disease mortality in men, but not women. Serum DHEA levels are directly associated with HDL levels in men, while conflicting evidence exists for a relationship between LDL and DHEA levels in women.
- This inverse relationship in men, observed in epidemiologic studies of 510 men and 289 women by Barrett-Conner et al (1986; 1987), and 236 men and 318 women by Nafziger et al (1990), was also found by Herrington et al (1990) who studied 103 men and 103 women prior to coronary angiography.

DHEA (or its metabolites) has been investigated as a treatment for a number of different indications, including post menopausal symptoms of hot flashes and depression; hyperlipidemia and the prevention of atherosclerosis, Alzheimer's Disease, potential immunomodulation (e.g., AIDS, stress or age induced immunosuppression).

1.3 Role Of DHEA In SLE

Three separate studies have explored the effect of DHEA treatment in the NZB/W murine model of SLE. Delay in the appearance of anti ds DNA antibodies and onset of nephritis with resultant decrease in mortality have been observed at dosages of DHEA comparable to those proposed for use in human SLE. New Zealand Black (NZB) and New Zealand White (NZW) F1 mice develop a lupus like disease. Female NZB/NZW F1 mice develop nephritis and die earlier than their male littermates. Studies have shown administration of androgens resulted in delayed formation of anti ds DNA antibodies (Siiteri et al, 1980; Roubinian et al, 1977; Roubinian et al, 1979a) and increased survival in hybrid NZB/NZW mice. (Melez et al, 1980; Roubinian et al, 1979b). Experiments with murine and human cells have shown that DHEA is capable of altering the profile of cytokine secretion. DHEA may be an important regulator of the immune system by up regulating IL2 secretion by activated T cells as demonstrated in both murine and human in vitro assays. (Daynes et al, 1990a; Suzuki et al, 1991)

1.4 Clinical Studies of DHEA

DHEA has been well tolerated in studies which treated at least 636 patients. Other than the undesired effects of androgen therapy in women, including hirsutism and acneiform dermatitis, there exist few reports of adverse events with administration of DHEA or DHEA-S. In men, there appears to be little or no change in serum testosterone, estrogen or androstenedione levels. With regard to the potential detrimental effect of chronic androgen therapy in normal premenopausal women, there is little data. One report, however, suggests that chronic oral administration of testosterone in high doses for 6 to 12 months to premenopausal female transsexuals does not alter adrenal steroidogenesis (Futterweit et al, 1992).

From data reported in a total of 124 men and 174 women the clinical pharmacokinetics of exogenously administered DHEA can be well characterized. Following oral administration DHEA is rapidly absorbed through the stomach and intestine, and converted in the liver to DHEA-S. Oral doses are approximately equipotent to intravenous dosing (Slaunwhite et al, 1967). Both DHEA

and DHEA-S circulate in the blood stream bound to protein, predominantly albumin, to some extent globulin, and only weakly to sex steroid hormone binding globulin (Meikle et al, 1991). DHEA-S has a long half life of approximately 10 hours, and its clearance is unaffected by age. It is continuously hydrolyzed, accounting for approximately 28% of the pool of free DHEA. The circulating half-life of DHEA is approximately 25 minutes; it is sulfated to DHEA-S constantly. The plasma concentration of DHEA-S is highly correlated with levels of urinary 17 ketosteroids. After IV administration of labelled DHEA or DHEA-S, most of the excretion is urinary. Fifty percent (50%) of a labelled dose of DHEA was eliminated within 8 days; 94% in the urine and 6% in the feces (Nyholm et al, 1979).

The metabolism of DHEA and DHEA-S appears to be significantly different in men and women and differs as well in premenopausal compared with postmenopausal women. In women, exogenously administered DHEA and DHEA-S are metabolized to androstenedione, testosterone and estrogens. DHEA-S from the intravascular pool appears to serve as a prehormone for ovarian production of sex hormones (Haning et al, 1991). In postmenopausal women, a smaller portion of exogenously administered DHEA or DHEA-S is converted to estrogens (Adams et al, 1971; Mattson et al, 1980; Schumann et al, 1970). It appears that the administration of exogenous DHEA/DHEA-S to postmenopausal women may result in a higher degree of conversion to testosterone and other androgens than in premenopausal women and in men. (Mortola et al, 1990; Calabrese et al, 1990; Morales and Yen; personal communication).

Morales and Yen (personal communication) administered 50 mg of DHEA daily to 30 older men and women and found a transformation of DHEA to androgens in the women only. Testosterone, androstenedione and dihydrotestosterone doubled over pretreatment values measured in the women while the men showed no increases in androgen levels. In general, following low oral doses of exogenous DHEA or DHEA-S up to 100 mg/day, serum levels of testosterone and androstenedione are unchanged in men (Drucker et al, 1972; Morales and Yen; personal communication). Administration of much larger oral doses of 750 to 2250 mg per day for 1 to 4 months to men resulted in modest increases in serum DHEA-S levels of 2.5-10 fold (Nestler et al, 1988; Usiskin et al, 1990; Welle et al, 1990; Dyner et al, 1993).

There is experience reported in the literature of the use of DHEA or DHEA enanthate plus estrogen administered IM in approximately 500 postmenopausal women. In the largest series, by Jurczek (1976), 386 patients received treatment for as long as 4 years. There were no reports of voice change or hirsutism; endometrial hyperplasia was not observed, and cytologic examinations did not suggest an androgenic effect. Transient mastodynia was reported.

Administration of DHEA-S intravenously or intra-amniotically to pregnant women does not appear to result in adverse effects upon either mother or fetus. In a series of 111 normal vaginal deliveries, administration of DHEA-S to 24 patients resulted in elevation of maternal serum estradiol levels at 0, 6, 12, 24 and 36 hours after delivery (Aisaka et al, 1984). Lactation was significantly decreased on the second day, but had normalized on the third day. These observations suggest that transient inhibition of lactation is caused by the effect on the mammary glands of the elevated estrogens converted in the placenta from administered DHEA-S.

1.5 Clinical Studies of DHEA in SLE

On the basis of these observations, studies were initiated at Stanford to study DHEA in patients with mild to moderate lupus. Two (2) studies of the safety and therapeutic potential of DHEA in

patients with mild to moderate lupus have been initiated to date. These studies were conducted by Drs. Ronald van Vollenhoven and James McGuire, Stanford University (Sponsor).

Phase I Study (ongoing): In an open label, Phase I study, 15 premenopausal female patients with active mild to moderate SLE received 200 mg/day of DHEA for 3 months in addition to indicated therapy with prednisone, hydroxychloroquine and NSAIDs (van Vollenhoven et al, 1993). Six patients continued treatment with DHEA for a total of 6 months. Outcome measurements included SLE Disease Activity Index (SLEDAI) scoring and disease severity evaluation by patient and physician assessment of well being by visual analog scale (VAS).

Patient assessments, by VAS or SLEDAI, were considered changed if the value differed by at least 10% from baseline. Preliminary analysis of the data from this study showed that after 3 months, SLEDAI scores improved in 9 patients (60% of patients), worsened in 5 patients (33%) and were unchanged in 1 patient (7%). Patient overall assessments had improved in 10 (67%) and worsened in 2 (13%), while physician overall assessments had improved in 7 (47%) and worsened in 4 patients (25%). Of the 8 patients treated with systemic glucocorticoids at the initiation of the trial, 6 (75%) were able to discontinue or reduce the dose of glucocorticoids by a clinically important amount (20% or greater). The average prednisone dose was reduced from 20.0 ± 4.4 mg/day to 13.9 ± 3.5 mg/day ($p < 0.02$).

Six (6) patients have now completed 6 months of treatment with DHEA. Compared with original baseline values, SLEDAI scores were improved in 5 (83%) and worsened in 1 patient (17%). Patient and physician overall assessments were improved in 4 patients (67%). Of the 6 patients, 4 were being treated with corticosteroids at the beginning of the trial and in each a meaningful reduction of the dose or discontinuation was possible during DHEA treatment. Average daily prednisone dose was reduced from 23.1 ± 9.1 mg/day to 8.5 ± 4.1 mg/day ($p < 0.01$). Anecdotally, 1 patient experienced a dramatic drop in proteinuria, from 6 to 8 gm/24 hours at baseline to 1.4 gm/24 hours at 3 months and 0.4 gm/24 hours at 6 months. Thrombocytopenia resolved in another patient.

Overall, DHEA was well tolerated. Adverse events included acneiform dermatitis in 8 of 15 patients (53%). One patient discontinued due to this adverse event, while other patients who showed a beneficial response to DHEA elected to decrease their dose from 200 mg/day to 100 or 50 mg/day and experienced resolution of the event. Hirsutism was observed in 2 of 15 patients (13%) and a transient increase in libido was noted by 1 patient (7%).

Phase II Study: This study consisted of two parts. The first part was designed as a double-blind, randomized, placebo-controlled study in patients with mild to moderate SLE (van Vollenhoven et al, 1993; Gorelick et al, 1993). Patients were randomized to receive DHEA, 200 mg daily or matching placebo. The original eligibility criteria allowed adult female patients who were on a stable regimen of nonsteroidal anti-inflammatory drugs, hydroxychloroquine, or low dose glucocorticoids (prednisone, ≤ 10 mg/day, or equivalent), with disease manifestations under satisfactory control, a diagnosis of SLE by ACR criteria, who were able and willing to exercise a reliable form of primary birth control and no or minimal renal involvement, defined as a normal urinalysis or no more than 1+ proteinuria, stable for at least six months, with serum creatinine level (or creatinine clearance) within the normal range¹ to enroll in the study. After completing three months in the double-blind portion of the study, patients and physicians were unblinded. Patients were then offered the opportunity to receive DHEA in an open label continuation protocol.

¹Deleted by amendment 1/7/92, which allowed for randomization stratified by presence or absence of renal disease.

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Thirty patients were randomized and 28 were evaluable. Treatment groups were well matched in baseline characteristics in age, sex, ethnicity, months from SLE diagnosis and months from first SLE symptoms. However, in examining baseline characteristics of disease severity (SLEDAI score, patient self assessment, physician assessment, prednisone dose), there were differences between treatment arms in baseline SLEDAI and prednisone dose. SLEDAI score for patients on DHEA was 9.8 ± 1.7 vs. 6.1 ± 1.3 for those patients on placebo ($p = 0.10$). The prednisone equivalent dose was 15.8 ± 3.0 mg/day for DHEA and 7.7 ± 1.2 mg/day for placebo, $p = 0.06$.

Of the 14 evaluable patients randomized to receive DHEA, 11 continued in the open label phase of the protocol and 3 patients discontinued (1 due to an adverse event, 1 due to lack of efficacy, and 1 due to other reasons). Of the 14 randomized to placebo treatment, 11 elected to receive DHEA in the open label phase and 3 patients discontinued (1 whose disease was in remission and 2 elected not to enter the open label phase).

The most commonly described adverse events in the double-blind phase were acne, reported in 8/14 patients randomized to DHEA treatment and 1/14 in the placebo group, and hirsutism, in 2/14 DHEA-treated and 4/14 placebo-treated patients. Other adverse events attributed to study drug included emotional lability, menometrorrhagia, rash and weight gain. In general DHEA was well tolerated during the blinded phase of the protocol, necessitating 1 withdrawal due to adverse events in the DHEA treated group. Details on adverse events are in the Investigational Drug Brochure.

After the three month blinded study, patients could elect to continue (or begin) open label treatment with DHEA. During the open label phase, 5/22 patients complained of acne and/or hirsutism. Three patients withdrew due to these complaints during the open label phase. Other adverse events included emotional lability (1 placebo randomized patient on open label drug).

An analysis of the effect of DHEA administration during the three month double blind phase was performed by comparing the value of each outcome (disease activity by SLEDAI score, patient and physician assessment and glucocorticoid dose) at month 3 to baseline. For each of the four efficacy variables, the mean value for the DHEA treated group improved (decreased) and the mean for the placebo group worsened (increased).

Because of differences in baseline efficacy parameters between treatment groups, the primary analysis was an ANOVA adjusted for covariates. These results are presented in Table 1.

Table 1: Changes from Baseline at Month 3 for Primary Outcome Measures (Mean \pm SEM)

	DHEA (n=14)		Placebo (n=14)		p value	
	Baseline	Change	Baseline	Change	unadj. ²	adj. ³
SLEDAI	9.8 (1.7)	-1.7 (1.2)	6.1 (1.3)	0.8 (0.7)	0.09	0.21
Patient Assess	39.4 (6.3)	-11.5 (5.7)	42.9 (6.6)	2.4 (7.0)	0.14	0.002
Physician Assess	21.4 (4.6)	-3.1 (3.8)	21.4 (4.0)	1.1 (4.2)	0.47	0.32
Glucocorticoid	12.4 (3.2)	-3.2 (1.7)	5.3 (1.4)	2.0 (2.6)	0.11	0.31

²T test, 2-sided.

³ANOVA, adjusted for baseline, baseline SLEDAI, baseline prednisone dose and (except for glucocorticoid) changes in prednisone dose.

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Change from baseline in all parameters evaluated was better in the DHEA-treated patients, although statistical significance was achieved only for patient assessment.

During the blinded portion of the protocol, a flare of the underlying SLE occurred in 8/14 placebo patients (57%) and 3/14 DHEA patients (21%) ($p=0.053$, χ^2).

Data from the three month double-blind, randomized treatment period suggest that DHEA, administered orally in daily doses of 200 mg, is generally well tolerated, and may have steroid sparing effects in patients with mild to moderate SLE. Complaints of acne and/or hirsutism were common in both treatment groups, and necessitated cessation of therapy in only one patient. During open label continuation of treatment, 3/22 patients dropped out because of acne or hirsutism. Other reported adverse events associated with the use of study drug and not the underlying SLE disease activity were as commonly reported in the placebo as the active treatment population.

This protocol is for the treatment of SLE with daily oral doses of 100 to 200 mg DHEA. This represents a relatively small pharmacologic dose of DHEA, more consistent with hormone replacement rather than high dose therapy or very high dose treatment with anabolic steroids. It can be anticipated that hormone metabolism in patients receiving DHEA would respond and adapt to small pharmacologic doses of DHEA, to produce the desired clinical outcome in SLE. The clinical safety data from the Stanford studies and other clinical trials are consistent with the conclusion that the toxicity of DHEA is limited to its steroidal pharmacology and that when used at the proposed doses should be reasonably safe for use in patients with SLE. The duration of the study will be 7-9 months. This study duration will allow patients who enroll in the protocol with the highest dose of prednisone allowed (30 mg/day) adequate time to reduce their prednisone dose to ≤ 7.5 mg/day and sustain that level for 2 months. For those patients who are able to reduce their dose to ≤ 7.5 mg/day after either 6 or 7 months on treatment, but will need to sustain this level for 2 additional months, the duration of the protocol will be extended two additional months, for a total of 8 or 9 months of dosing.

2. STUDY SYNOPSIS

This study is designed as a double-blind, randomized, placebo-controlled trial to evaluate 2 different treatment regimens of GL 701 (DHEA): 100 or 200 mg/day versus placebo in patients with mild to moderate prednisone-dependent systemic lupus erythematosus. A total of 190 patients will be enrolled in this study. An interim analysis with the purpose of determining adequacy of sample size will be conducted, and based on this analysis the total number of patients will be adjusted. Patients will be enrolled in approximately 15 centers. Enrollment is expected to last 6 to 12 months.

Efficacy will be defined in terms of reduced requirement for prednisone therapy based on disease activity assessed by SLEDAI score. Every effort will be made to taper prednisone in the face of stable or improving manifestations of SLE.

The goals of this study are to evaluate the safety and efficacy of GL701 in patients with SLE and to examine its pharmacokinetics. Patients will be required to have a screening and qualifying visit before randomization. They will return to the clinic monthly for the remaining 7 to 9 months.

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Severity of disease exacerbations will be assessed exclusively by the level of treatment required. Severe disease will be that which requires ≥ 1 mg/kg/day of prednisone or use of immunosuppressive agents.

Evaluations will include monthly physical examinations and laboratory determinations, SLE Disease Activity Index (SLEDAI), patient and physician overall assessments by Visual Analog Scale (VAS), health status and fatigue assessments, and at baseline and end of the study the SLICC Damage Index.

Patients who complete this protocol (GL94-01) will be eligible to continue to receive DHEA (GL701) in a subsequent study to evaluate the safety of long term dosing.

3. OBJECTIVES

In patients with mild to moderate, prednisone dependant SLE:

- 3.1 Evaluate the safety of different dosages of GL 701: 100 mg/day or 200 mg/day vs. placebo.
- 3.2 Assess the effectiveness of different dosages of GL 701 vs. placebo.
- 3.3 Assess the pharmacokinetics of GL 701 following oral administration.

4. PATIENT ELIGIBILITY

4.1 Inclusion Criteria

- 4.1.1 Women who have a diagnosis of Systemic Lupus Erythematosus according to the American College of Rheumatology Criteria (Appendix 11.1).
- 4.1.2 Patients with mild to moderate disease characterized by a prednisone⁴ dose of ≥ 10 and ≤ 30 mg/day and either
 - a) In the last 12 months have attempted to taper prednisone dose but failed and have had a stable prednisone dose for at least 6 weeks preceding the study
 - or
 - b) In whom there has been no attempt to taper in the last 12 months and have had a stable prednisone dose for at least 3 months preceding the study.
- 4.1.3 Patients treated with NSAIDs and/or Plaquenil must be on a stable dose with no change in dose for at least 1 month preceding the study.

⁴Where prednisone is specified, any glucocorticoid may be used providing equivalent dosages are used as listed in Appendix 11.3.

- 4.1.4 Patients must be at least 18 years of age.
- 4.1.5 Women of child-bearing potential must have a negative pregnancy test (within 2 weeks prior to study entry) and use reliable form of birth control excluding estrogen containing oral contraceptives while participating in the study.

4.2 Exclusion Criteria

- 4.2.1 Male patients.
- 4.2.2 Patients on < 10 mg/day or > 30 mg/day of prednisone.
- 4.2.3 Patients on alternate day prednisone dosing regimens. These patients must convert to daily dosing regimens and be stable for 6 weeks prior to study to be eligible.
- 4.2.4 History of breast cancer or malignancy of the reproductive tract organs.
- 4.2.5 Patients receiving treatment with ACTH within the 3 months preceding study entry.
- 4.2.6 Patients receiving prednisone \geq 1 mg/kg/day or immunosuppressive therapy.
- 4.2.7 Patients on cyclophosphamide, azathioprine, other immunosuppressive agents or IVIg within the last 3 months.
- 4.2.8 Patients receiving androgens within the 3 months preceding study entry.
- 4.2.9 Patients with known hypersensitivity to DHEA or the inactive ingredients used in formulating GL701 (cornstarch, lactose, magnesium stearate).
- 4.2.10 Patients who participated in the double-blind DHEA study at Stanford University.
- 4.2.11 Participation in other clinical studies, including use of investigational agents within the longer of 30 days or 10 half lives of the agent.
- 4.2.12 Any condition which in the investigator's opinion is sufficient to prevent adequate compliance with the study.
- 4.2.13 Inability of patient to provide written informed consent.

4.3 Qualification for study

Once written informed consent is obtained, patients will have a screening visit and laboratory evaluations performed to determine if they qualify for the study. A patient is enrolled in the study once all eligibility criteria are met.

No change in dosage of prednisone, NSAIDs or Plaquenil will be allowed between Screening and Qualifying visits.

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4.4 Assignment of Treatment

After qualifying for the study, patients will be randomly assigned to receive one of 3 treatments: placebo, or GL 701: 100 mg/day or 200 mg/day.

4.5 Treatment Period

All patients will receive study medication (GL701 or placebo) for at least 7 months. During this time, every effort will be made to taper the prednisone dose (according to schedule, see section 5.2) to ≤ 7.5 mg/day in the face of stable or improving manifestations of SLE.

If a patient has not been able to reduce her prednisone dose to ≤ 7.5 mg/day at the end of the 7 months of dosing, then she will exit the study.

If a patient has successfully decreased her prednisone dose to ≤ 7.5 mg/day and has sustained this level for at least 2 months prior to the end of the 7 months of dosing, then she will exit the study.

If however at the end of 6 or 7 months of dosing a patient has successfully reduced her prednisone dose to ≤ 7.5 mg/day but has not yet sustained this lower dose for 2 months, she will continue to receive study medication for 2 additional months (total of 8 or 9 months of dosing, respectively) or until prednisone dose increases to > 7.5 mg/day whichever comes first. Once this occurs she will exit from the study.

5. STUDY DRUG ADMINISTRATION

5.1 GL701

5.1.1 GL 701 is Genelabs' formulated version of Dehydroepiandrosterone (DHEA).

5.1.2 Drug Supply: Study medication will be supplied in hard, gelatin capsules. Each capsule contains either 50 mg DHEA or placebo. Four capsules of study medication are to be taken each morning. Study medication is to be stored at room temperature, 59-86°F in a dry place.

Formulation for study medication contains lactose. Each GL701 capsule will contain 50 mg DHEA, and approximately 280 mg of excipients including cornstarch, lactose, magnesium stearate.

Each placebo capsule will contain approximately 330 mg of cornstarch, lactose, magnesium stearate.

5.1.3 Drug Packaging: Study medication will be packaged in envelopes containing blister packs. On the outside of each envelope will be a label identifying a patient number and visit week. Each envelope will contain 2 blister packs (a total of 4 weeks of study medication). Each blister pack will contain enough medication for 14 days (4 capsules/morning) and will be labelled with Day 1 through Day 14. In addition, each blister pack contains 2 days of overage labelled "extra." All four

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capsules of study medication are to be taken each morning.

- 5.1.4 Medication will be packaged in a blinded manner. Patients on all treatment arms will take 4 capsules each morning: GL 701 200 mg/day (four 50 mg DHEA capsules), GL 701 100 mg/day (two 50 mg DHEA capsules, 2 placebo capsules), or placebo (4 placebo capsules).
- 5.1.5 Each monthly envelope will contain a double-blind label specifying the study number, patient number, and directions for use. This double-blind label will have a portion permanently affixed to the envelope, and a tear off portion to keep in the pharmacy. In the event of an emergency that requires the unblinding of a patient's treatment code, the covered section of the tear off portion of the label can be swabbed with alcohol to reveal the treatment code of the patient and the lot number of the medication. Genelabs and the Independent Monitoring Board should be notified immediately if any patient is unblinded and unblinding should be noted in the case report form.

5.2 Changes in Prednisone Dose

- 5.2.1 Prednisone dose must be reduced if disease activity is stable or improved by SLEDAI score since the prior monthly visit. Prednisone must be tapered according to the following schedule:

<u>If daily Prednisone dose is:</u>	<u>Dose Reduction is:</u>
>0 ≤ 5 mg	1 mg/day
>5 mg ≤ 10 mg	2.5 mg/day
>10 mg ≤ 30 mg	5.0 mg/day
> 30 mg	Taper at Investigator's discretion

- 5.2.2 If the SLEDAI score has worsened (increased) since the prior monthly visit, the daily dose of prednisone may be increased at the investigator's discretion.

5.3 Concomitant Medications

- 5.3.1 No other investigational medications may be taken during the study.
- 5.3.2 No immunosuppressive agents may be taken during the study.
- 5.3.3 If a patient requires an increase in prednisone dose to ≥ 1 mg/kg/day or the addition of an immunosuppressive agent, the patient must discontinue study treatment. See Early Treatment Termination section 6.7.
- 5.3.4 No changes from baseline (study entry) are allowed for dosages of Plaquenil (hydroxychloroquine) or NSAIDs except for documented drug toxicity.

5.3.5 Patients who develop acneiform dermatitis should be treated with topical agents.

6. STUDY ACTIVITIES

6.1 Screening

- 6.1.1 Obtain informed consent and distribute patient information sheet.
- 6.1.2 Review general Medical History and SLE Specific Medical History including any significant prior organ system involvement.
- 6.1.3 Complete ACR Criteria for diagnosis of SLE.
- 6.1.4 Review past treatment history including the use of glucocorticoids and immunosuppressive agents.
- 6.1.5 Physical exam including vital signs, weight and height for body mass index.
- 6.1.6 SLICC Damage Index by physician.
- 6.1.7 Anti-ds DNA.
- 6.1.8 Complement Levels: C3, C4.
- 6.1.9 Serum Chemistry including SGOT, SGPT, creatinine, cholesterol, triglycerides, LDL and HDL. Patient should be fasting for at least 8 hours before labs are drawn at baseline. Pregnancy test at screening for females only.
- 6.1.10 CBC with platelet count.
- 6.1.11 Urinalysis with microscopic analysis.
- 6.1.12 24 hour urine for creatinine clearance and protein quantitation.
- 6.1.13 Anti-nuclear antibodies (ANA).
- 6.1.14 Serum Levels of 17 β Estradiol, Testosterone.
- 6.1.15 Serum levels of FSH, LH.
- 6.1.16 Anti-phospholipid antibodies
- 6.1.17 Serum samples for levels of DHEA-S (Pediatric tubes preferred) and for banking--sent to Genelabs. Results will not be returned to investigators until the study is complete.
- 6.1.18 12 lead electrocardiogram (EKG).

- 6.2 Qualifying Visit (Initial Dosing Visit with Qualification) - Week 0**
(should occur as soon as possible after screening evaluations but must occur within 10 days of Screening Visit)
- 6.2.1 Confirm that all eligibility criteria are met (see Inclusion Criteria section 4.1 and Exclusion Criteria section 4.2).
 - 6.2.2 Concomitant Medication Review (NOTE: changes in prednisone dose are not permitted at this visit. If a dose change is required, the patient must discontinue study and be reevaluated after receiving a stable dose for at least 6 weeks.)
 - 6.2.3 Adverse Event Assessment.
 - 6.2.4 SLEDAI scoring by physician.
 - 6.2.5 Assessment of health status and fatigue by patient.
 - 6.2.6 Global assessment of disease activity utilizing a 10 cm VAS scale by patient and physician.
 - 6.2.7 If patient qualifies at this visit based on laboratory and clinical evaluations, study medication will be dispensed. Explain study medication dosing and packaging. Patient will begin taking study medication the morning following this visit.
 - 6.2.8 Schedule patient for laboratory evaluations not more than 10 days prior to Visit 1- (Week 4).
- 6.3 Dosing Visit 1 - Week 4**
- 6.3.1 Adverse Event Assessment.
 - 6.3.2 Concomitant Medication Review including change in glucocorticoid dosing.
 - 6.3.3 Physical exam including vital signs, weight.
 - 6.3.4 Disease Assessment as in 6.2.4 to 6.2.6.
 - 6.3.5 Laboratory evaluations as in 6.1.7 to 6.1.11, 6.1.17.
 - 6.3.6 Dispense Study Medication and collect used packaging and any unused study medication from previous visit.
 - 6.3.7 Schedule patient for laboratory evaluations not more than 10 days prior to Visit 2- Week 8.

6.4 Dosing Visits 2 through 6 - Weeks 8, 12, 16, 20, 24 and in the event of delayed reduction in prednisone (see section 4.5), Dosing Visits 7 and 8 (Weeks 28 and 32)

Same as section 6.3 excluding lab 6.1.17.

6.4.1 Reminder: Schedule patient for laboratory evaluations not more than 10 days prior to each visit. Patients should take their study medication after laboratory specimens are drawn.

6.5 Completion Visit or Termination Visit

6.5.1 Labs: Same as 6.1.7 to 6.1.17. Patients should be fasting for at least 8 hours before specimens are drawn.

6.5.2 Disease activity assessments: 6.1.6 and 6.2.4 to 6.2.6.

6.5.3 Physical exam including vital signs, weight.

6.5.4 Adverse Event Assessment.

6.5.5 Concomitant Medication Review.

6.5.6 Treatment Completion / Termination forms.

6.6 Follow up for All Patients

All patients are encouraged to undergo follow up as below.

6.6.1 Patients who complete study GL94-01 according to protocol will be eligible for dosing in a subsequent study.

6.6.2 Patients who complete study GL94-01 according to protocol and who do not wish to continue to receive GL701 will be asked to return for a follow up evaluation visit 12 months after the Qualifying Visit.

6.6.3 Patients who withdraw from the study for any reason will be asked to return for follow up evaluation visits at 7 months and 12 months after the Qualifying Visit.

6.7 Conditions for Early Termination from the Study

Interruption of study treatment is not allowed.

Patients who discontinue treatment early will be classified into one of the following categories. If unblinding occurs due to severe adverse events, then the unblinding will be noted.

- 6.7.1 Termination due to lack of efficacy
 - 6.7.1.1 Patient's SLE disease activity required treatment with prednisone in doses ≥ 1 mg/kg/day.
 - 6.7.1.2 Patients SLE disease activity required treatment with an immunosuppressive agent.
 - 6.7.1.3 Investigator terminated study treatment because of lack of efficacy.
 - 6.7.1.4 Patient withdrew from study because of lack of efficacy.
- 6.7.2 Termination possibly related to safety of study treatment
 - 6.7.2.1 Investigator terminated study treatment because of adverse events possibly related to study treatment.
 - 6.7.2.2 Patient withdrew from study because of adverse events possibly related to study treatment.
 - 6.7.2.3 Patient died from causes possibly related to study treatment.
- 6.7.3 Termination for reasons not related to efficacy or safety of study treatment.
 - 6.7.3.1 Investigator terminated study treatment for reasons not related to efficacy or safety of study treatment.
 - 6.7.3.2 Patient withdrew from study because of reasons not related to efficacy or safety of study treatment.
 - 6.7.3.3 Patient died from causes not related to safety of study treatment.
 - 6.7.3.4 Patient was lost to follow-up
 - 6.7.3.5 Termination for other reasons not related to efficacy or safety of the study treatment.
 - 6.7.3.6 Patients requiring treatment with ≥ 1 mg/kg/day prednisone for other reasons.

Patients who terminate from the study prematurely will not be eligible to receive further treatment with GL701 in the follow up study to GL94-01.

7. ADVERSE EVENTS

- 7.1 Definitions which apply are as follows:

7.1.1 "Serious adverse experience" means any experience that suggests a contraindication, side effect, or precaution.

With respect to human clinical experience, a serious adverse experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

7.1.2 "Associated with the use of the drug" means that there is a reasonable possibility that the experience may have been caused by the drug.

- 7.2 All adverse experiences occurring during active participation in the study must be reported and assessed on Case Report Forms, regardless of severity and regardless of whether thought to be related to the study drug. Report will include description of the severity, duration and outcome of the experience and the Investigator's opinion of the relationship of the experience to the study drug in the format required by the Case Report Form.
- 7.3 Any adverse experience occurring during active participation in the study which is serious, life-threatening or fatal must be reported by telephone to the Sponsor within one working day of its occurrence.
- 7.4 Mild or moderate adverse experiences thought to be possibly or probably related to the study drug must be reported to the Sponsor within 10 working days of their occurrence, unless they are "expected", i.e. listed in the Investigational Drug Brochure (IDB).
- 7.5 All patient deaths during the study must also be described in brief narrative form by the Investigator on the Death Report page provided in the Case Report Form (CRF). Description will include Investigator's assessment of relationship to the study drug.

7.6 Reporting to Sponsor

Serious, Life-Threatening or Fatal	One (1) working day (by telephone)
Mild or Moderate if Possibly or Probably Associated with Drug (except "expected" in IDB)	Ten (10) working days
All events	CRF

7.7 Sponsor Phone Numbers

Medical Monitor Kenneth Gorelick, M.D	Work #: 415-369-9500 *Pager PIN #: 811-0502
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Director, Medical Operations Arlene Kunz	Work #: 415-369-9500 *Pager PIN #: 110-2372
Clinical Research Associate Kari Barbu	Work # 415-369-9500 *Pager PIN #: 811-0504
Genelabs Incorporated	FAX #: 415-368-3198
*Pager #: 1-800-946-4646	

8. STUDY ADMINISTRATION

8.1 Institutional Review Board

This study must have the approval of a properly constituted Institutional Review Board (IRB) or Committee recognized by the FDA for approving clinical studies.

Before the investigational drug will be shipped to the Investigator, the Investigator will provide the Sponsor with a copy of the IRB approval letter stating that the study protocol and informed consent form have been reviewed and approved by the IRB.

Serious, life-threatening, or unexpected adverse experiences, and any critical new study information must also be reported to the IRB by the Investigator. The investigator should comply with the reporting requirements of their IRB.

8.2 Informed Consent

It is the responsibility of the Investigator to design the informed consent form according to appropriate Federal Guidelines (21 CFR 50).

The consent form must be approved by the Institutional Review Board. The Sponsor requests review of the consent form prior to IRB submission. A copy of the approved form must be submitted to the Sponsor prior to the initiation of the study.

State and local laws, and institutional requirements may require the disclosure of additional information on the informed consent form and many allow for different methods of obtaining consent other than written signature by the patient.

A copy of the signed informed consent form must be given to the patient. The Investigator must keep each patient's signed consent form on file and readily available for review by the Study Monitor and for FDA inspection at any time.

8.3 Drug Accountability

Each shipment of drug supplies for a study will contain Clinical Supplies Shipment forms to assist the Investigator in maintaining current and accurate inventory records. This form identifies the quantity of drugs contained in the shipment to the study center, as well as the lot and protocol number for the drug. All shipment contents should be verified against this

information. Any discrepancies between the drug received and the shipping forms information, as well as any damage to the shipment should be noted on the shipping form. One copy of the form should be kept with the drug accountability records for the site, and the remaining form should be signed as receipt verification and returned to Simirex.

Drug Accountability Records should cover receipts, dispensing, and return of study drug supplies. Separate inventory records should be kept for each study performed at the site. Drug is labeled with a specific study number and should not be dispensed for use in other investigational studies. For accurate accountability, the following information must be noted on the Drug Inventory Sheet when drug supplies are used during the course of the study: the identification number of the subject to whom the medication is dispensed, the date drug is dispensed and quantity of drug dispensed. Inventory records must be readily available for inspection by the CRA and are open to FDA inspection at any time.

The GL701 drug supply will be packaged in a blinded manner and shipped from Simirex to the sites. Only authorized personnel designated by the Principal Investigator should have access to the drug. Study medication should be stored at room temperature (59-86°F) in a dry place.

All packaging and partially used and unused drug supplies will be returned to Simirex. Return of all drug supplies must be coordinated with the CRA prior to shipment. When either used or unused drug supplies are to be returned, the Pharmacist should record the number of used and/or unused blister packs and lot numbers being returned on the Drug Inventory Sheet, and complete the Return of Clinical Investigational Material form provided by the CRA.

Upon completion of this study, the Investigator and Pharmacist should verify and sign that all drug supplies, including all used blister packs, have been returned for each study subject and that no drug supplies remain in the Investigator's possession. If all drug supplies are not returned, the Investigator must include an explanation and document all attempts to have the supplies returned. A copy of the Drug Inventory Sheets will be collected by the CRA.

Return Used and Unused Blister Packs To:

Simirex Inc.
12000C Commerce Parkway
Mount Laurel, NJ 08054

8.4 Record Retention

It is the responsibility of the Investigator and the study staff to maintain a comprehensive and centralized filing system of all documentation relevant to the study. Such documentation includes:

- 8.4.1 Case Report Forms – must be legible, accurate and up to date with copies of the corrections.

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- 8.4.2 Patient Files – should substantiate the data entered in the Case Report Forms including laboratory data, patient histories, treatment regimens, physical examinations, concomitant medications, and any adverse events.
- 8.4.3 Patient Non-Qualifier Log – should record the reason any patient was screened for the study and found to be ineligible.
- 8.4.4 Drug Dispensing Log – should record the total amount of medication received from and returned to the Sponsor, and the amount distributed to and returned from the patient. (see section 8.3.) This information must agree with the information entered in the Case Report Forms.
- 8.4.5 Informed Consent Forms – completed consent forms from each patient must be available and verified for proper documentation.
- 8.4.6 Informed Consent Log - should record the date, initials, and study number (if applicable) of any patient who signed an Informed Consent or has any other documentation of giving consent.

Protocols and protocol amendments and their IRB approvals, revised 1572 forms, all correspondence, and any other documents pertaining to the conduct of the study, must be kept on file by the Principal Investigator for a minimum of 2 years after notification by the Sponsor of either FDA approval or discontinuation of the IND.

8.5 Case Report Forms

All data will be recorded on Case Report Forms provided by Genelabs Technologies, Incorporated. All entries must be legible and complete. Black ink must be used for completion of the forms.

All corrections must be initialed and dated by the Study Nurse or Investigator. Corrected copies of CRF's will be filed with the corresponding original.

Case Report Forms will be completed and collected on a timely basis. The original Case Report Forms will remain at the site until collected by the CRA.

8.6 Monitoring the Study

Individual sites will be monitored at appropriate intervals to assure satisfactory enrollment rate, data recording, and protocol adherence. The frequency of monitoring an individual site may vary depending on enrollment rate and the quality of data collected. The Investigator and staff are expected to cooperate with the CRA and provide all relevant study documentation in detail at each site visit on request for review by the CRA. In addition to these visits, each site may be monitored by phone to keep abreast of patient status and to answer questions.

8.7 Study Amendment

With concurrence of the Investigator, if the study needs to be amended, the Sponsor will

provide the Investigator with a protocol amendment document. Two signature pages will be sent, one for the site, one for Genelabs. One copy should be signed by the Investigator and returned to the Sponsor. A copy of the amendment and, if applicable, a revised consent form, must also be submitted for approval to the IRB by the Investigator. Deviations from the Protocol must be approved in writing by the Sponsor.

8.8 Final Study Report

The Investigator shall provide the Sponsor with a final report within 30 days following completion of the study center's participation in the investigation.

9. STUDY ANALYSIS

9.1 Baseline Comparability

Baseline values, including demographic variables and disease status, will be compared between the treatment groups by summary tables and by Cochran-Mantel-Haenszel test or ANOVA with stratification by or control for site. Variables attaining statistical significance levels less than 0.05 for association with treatment assignment may be included as covariables or stratifying variables in analysis.

The baseline value for all variables will be the last value measured or obtained prior to initiation of study treatment. Age is age on the day of first study treatment.

9.2 Blinding

Patients, investigators, all persons involved in running the study, and all employees of the sponsor except for a designated statistician are blinded to patient treatment assignments. No unblinding will take place until after all patients in the study have completed the blinded portion of the study and all data from the blinded portion of the study have completed all data verification and all data query resolution, including all classification of treatment terminations and resolution of data query issues surfaced during test runs of analysis programs.

Both patients and investigators will be asked at study termination to guess which treatment arm the patient was in. These results will be displayed and their possible affect upon study results will be assessed. The function of this analysis is to assess the degree to which differing side effect profiles could affect the double blind. If the treatment efficacy is so strong that patients or investigators can infer treatment from efficacy results then an association between actual treatment and guessed treatment is expected to occur.

All decisions regarding admissibility of data for any patient for analysis will be made prior to the unblinding to anyone of the treatment assignment for that patient. Since data questions may surface during analysis, this requires maintenance of the blind until final analysis programs have been tested on the group as a whole. Reasons for all data exclusions will be documented. Any data exclusion which has to be made after unblinding will be noted and explained and its impact on the results will be evaluated.

9.3 Efficacy

9.3.1 Patient Evaluability for Efficacy Analysis

Patients who terminate treatment prior to completing four months will be excluded from the primary analyses. These patients will be included in an intent-to-treat analysis only. Both the primary analyses and the intent-to-treat analyses will be terminal visit analyses. Reasons for any exclusions from any analysis will be thoroughly documented.

9.3.2 Primary Efficacy Variables

This study includes two primary efficacy variables. The two variables are

1. Achievement of a sustained decrease in prednisone dose to 7.5 mg/day or less, and this decrease must be sustained for no less than two months, and
2. Percent decrease in prednisone use, comparing final dose with baseline.

The first primary efficacy variable assesses clinically important reduction in daily prednisone use. This variable is specifically designed to reflect treatment's ability to provide benefit consistent with 21 CFR 312 Subpart E status.

The second primary efficacy variable assesses percent reduction achieved in daily prednisone use. This variable has been agreed upon by a panel of experts in the treatment of SLE to be the best single variable quantitative assessment of treatment benefit.

Reductions in prednisone use are expected to be without meaningful increase in SLEDAI because of the prednisone dose tapering rules, however this assumption will also be checked by secondary analysis.

Analysis of primary efficacy variable 1 will be by logistic regression analysis of the proportion achieving success controlling for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

Analysis of primary efficacy variable 2 will be by ANOVA with control for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

As noted above, all decisions regarding admissibility of data for analysis will be made prior to unblinding. Differences between the treatment groups in the distribution of early terminations, should such differences occur, will be assessed for possible effect on the primary outcome analyses. Intent-to-treat analyses will also be made. Differences between primary analyses and intent-to-treat analyses, should they occur, will be assessed regarding the generalizability of results. Tests will be two sided at alpha level .05.

9.3.3 Secondary Efficacy Variables

Secondary efficacy variables include

- 1) Time to increase in SLEDAI score
- 2) Change in SLEDAI
- 3) Change in quality of life assessment
- 4) Improvement in global assessment of disease activity utilizing a 10cm VAS scale by physician.
- 5) Improvement in global assessment of disease activity utilizing a 10cm VAS scale by patient assessment of disease severity
- 6) Improvement in body mass index
- 7) Improvement in lipid profile
- 8) Quantitative changes in renal function
- 9) Quantitative changes in hematologic function

Results will be displayed and analyzed if appropriate.

9.3.4 Power

Initial sample size is 190 patients randomized to treatment. Power calculations are performed for a sample size of 168, 56 in each arm. The difference of 22 approximately compensates for loss in power from having to control for site and from early withdrawals.

With respect to primary efficacy variable 1: a sample size of 56 evaluable patients in each arm gives a power of approximately 80% for the pair-wise two-sided tests of primary efficacy variable 1 at $\alpha=.05$ if the true probability of success on one treatment is .05 and the true probability of success on the other treatment is .22. The power is also 80% if the true probabilities are .10 and .30 or .20 and .44. The power is approximately 50% if the true probabilities of success are .05 and .16 or .10 and .24 or .20 and .37, respectively.

With respect to primary efficacy variable 2: A sample size of 56 patients in each arm gives a power of 80% for the pair-wise two-sided tests of primary efficacy variable 2 at $\alpha=.05$ if the true difference between the two treatments is 30 and the true within group between-patient standard deviation is 55.

The assumption that the true within group between-patient standard deviation is 55 is temporary until the limited interim analysis gives an estimate. Sample size will then be adjusted to ensure 80% power for a treatment effect of 30.

9.4 Safety

Changes in lab values and incidence of adverse events by treatment group will be displayed by descriptive statistics. If appropriate, differences between treatment groups will be compared by Cochran-Mantel-Haenszel test or by ANOVA of ranks or by Spearman rank correlation.

9.5 Interim analysis

A limited interim analysis will be performed in order to adjust the sample size to ensure adequate power for primary efficacy variable 2. The limited interim analysis will be carried out under the control of an independent study monitoring board and no information regarding interim treatment efficacy differences will be issued or used in the sample size

adjustment. In particular, no information regarding interim treatment differences will be released to anyone who is blinded to patient assignments.

The limited interim analysis study will provide an interim (pooled) estimate of the patient to patient variability within treatment groups for primary efficacy variable 2. The limited interim analysis will be scheduled for all evaluable data available for analysis on the date of the four month anniversary of the enrollment of the 95th patient. If results for at least 50 evaluable patients are not available at that time then the interim will be performed once results for 50 evaluable patients are available. Results regarding pooled within group between-patient variation in primary efficacy variable 2 will be used to adjust the sample size.

9.6 Sample Size Adjustment

The sample size will be adjusted to ensure adequate power to detect treatment effects upon primary efficacy variable 2.

The interim estimate of between-patient variability will be used to calculate the number of patients needed to give 80% power for the two-sided test at $\alpha=0.05$ if the true treatment effect on primary efficacy variable 2 is 30, i.e. if the true expected treatment induced percent reduction is greater by 30 than the true placebo value. If the re-estimated sample size estimate is less than 168 then the study will continue as planned, no reduction in sample size will occur. If the re-estimated sample size is greater than 168, then the sample size for the study will be increased accordingly in order to ensure an adequately powered study. All valid data from the study will be used in the final analyses; this is not the type of two stage design which eliminates some of the interim data from use in the final analysis.

The use of interim pooled between-patient variability results to adjust total sample size gives a type of two stage study design. Use of all study data in the final analysis of a two stage study maximizes power but may require an adjustment in the final significance level. Procedures for appropriate adjustment of the nominal final alpha will be developed and submitted by the sponsor for approval by the FDA statistician prior to the interim analysis.

9.7 Independent Study Monitoring Board

An independent study monitoring board (ISMB) will be created. The ISMB will perform the following functions:

1. Confidentially monitor key safety parameters for indications that the study should be terminated because of safety considerations.
2. Monitor the generation and confidentiality of the limited interim analysis used to re-estimate sample size.
3. Monitor and provide guidance on any issue related to patient's welfare and the validity of the study, including amendments to the protocol.

The ISMB will include appropriate medical and statistical expertise. ISMB members must be free from conflicts of interest. The ISMB will receive its information from the

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designated statistician who also performs the confidential limited interim analysis.

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11. APPENDICES

- 11.1 ACR Criteria for Diagnosis of Systemic Lupus Erythematosus
- 11.2 SLEDAI Score for Disease Progression
- 11.3 Equivalent Dosages of Glucocorticoids
- 11.4 Schedule of Events

APPENDIX 11.1 ACR Criteria for Diagnosis of Systemic Lupus Erythematosus

A patient may be diagnosed with systemic lupus erythematosus if they have 4 or more of the following 11 disorders.

Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid Rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight: by patient history or physician observation
Oral Ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
Serositis	<ol style="list-style-type: none"> a. Pleuritis--convincing history of pleuritic pain, or rub heard by physician, or evidence of pleural effusion b. Pericarditis--documented by EKG, or rub, or evidence of pericardial effusion
Renal Disorder	<ol style="list-style-type: none"> a. Persistent proteinuria > 0.5 g/day or >3 if quantitation is not performed b. Cellular casts--may be red cell, hemoglobin, granular, tubular or mixed.
Neurologic Disorder	<ol style="list-style-type: none"> a. Seizures-- in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, or electrolyte imbalance) b. Psychosis--in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, or electrolyte imbalance)
Hematologic Disorder	<ol style="list-style-type: none"> a. Hemolytic anemia--with reticulocytosis b. Leukopenia-- < 4,000/mm³ total on two or more occasions c. Lymphopenia-- < 1,500/mm³ on two or more occasions d. Thrombocytopenia--< 100,000/mm³ in the absence of offending drugs
Immunologic Disorder	<ol style="list-style-type: none"> a. Positive lupus erythematosus cell preparation b. Anti-DNA: antibody to native DNA in abnormal titer c. Anti-Sm: presence of antibody to Sm nuclear antigen d. False-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by T. pallidum immobilization or fluorescent treponemal antibody absorption test
ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome.

APPENDIX 11.2 SLEDAI Score for Disease Progression

Enter weight in SLEDAI score column if descriptor is present at the time of the visit or in the preceding 10 days.

<u>Wt.</u>	<u>Present</u>	<u>Descriptor</u>	<u>Definition</u>
8	<input type="checkbox"/>	Seizure	Recent onset. Exclude Metabolic, infectious or drug cause.
8	<input type="checkbox"/>	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	<input type="checkbox"/>	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	<input type="checkbox"/>	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	<input type="checkbox"/>	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	<input type="checkbox"/>	Lupus Headache	Severe persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	<input type="checkbox"/>	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	<input type="checkbox"/>	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	<input type="checkbox"/>	Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	<input type="checkbox"/>	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	<input type="checkbox"/>	Urinary casts	Heme-granular or red blood cell casts.
4	<input type="checkbox"/>	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	<input type="checkbox"/>	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	<input type="checkbox"/>	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	<input type="checkbox"/>	New Rash	New onset or recurrence of inflammatory type rash.
2	<input type="checkbox"/>	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2	<input type="checkbox"/>	Mucosal ulcers	New onset or recurrence of oral or nasal ulcerations.
2	<input type="checkbox"/>	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	<input type="checkbox"/>	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2	<input type="checkbox"/>	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	<input type="checkbox"/>	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	<input type="checkbox"/>	Fever	>38° C. Exclude infectious cause.
1	<input type="checkbox"/>	Thrombocytopenia	<100,000 platelets/mm ³ .
1	<input type="checkbox"/>	Leukopenia	< 3,000 White blood cells/ mm ³ . Exclude drug causes.

TOTAL SLEDAI SCORE (sum of the weights next to descriptors marked present)

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APPENDIX 11.3

Equivalent Dosages of Glucocorticoids

Compound	Equivalent Potency (mg)
Cortisone	25
Hydrocortisone (cortisol)	20
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Triamcinolone	4
Dexamethasone	0.75

March 14, 1994

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APPENDIX 11.4 GL 701 SCHEDULE OF EVENTS

PROCEDURE	VITIT # WEEK #	Screening	Qualifying	DOSING VISITS								(8) 32	Comp / Term 28, 32, 36 / other	
				0	1	2	3	4	5	6	7			
Medical History / Past Medication History		X												
Adverse Event review		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and Glucocorticoid use		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X
Disease Assessments:														
-SLEDAI (by physician)		X	X	X	X	X	X	X	X	X	X	X	X	X
-SF-36 Health Status Survey (by patient)		X	X	X	X	X	X	X	X	X	X	X	X	X
-Global VAS (by physician and patient)		X	X	X	X	X	X	X	X	X	X	X	X	X
-Damage Index (by physician)		X												X
Required Tests:														
-EKG		X												
Laboratory Testing:														
-Central lab														
a. Full testing (fasting, see requisition)		X												X
b. Routine testing														
-Genelab DHEA-S, banking		X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication:														
-Drug dispensed			X	X	X	X	X	X	X	X	X	X	X	X
-Return of packaging and unused drug			X	X	X	X	X	X	X	X	X	X	X	X

NOTE: Patients who discontinue study treatment prematurely will undergo the full Completion / Termination visit. These patients are also encouraged to undergo follow up at 7 months and 12 months after Qualifying Visit.

Protocol #GL94-01
March 14, 1994

Amendment #1
April 25, 1994

A Double-Blind, Randomized Phase II/III Study of GL701 in Female Patients with Mild to Moderate Systemic Lupus Erythematosus

I have received and read the Investigational Drug Brochure for GL701 dated 12/93, the protocol dated 3/14/94, the amendment dated 4/25/94, and the Statement of Investigator Obligations. I agree to undertake the study as defined therein. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved by Genelabs Technologies, Inc. and the Institutional Review Board. Failure to adhere to those stipulations may constitute a breach of federal regulations and may result in termination of the study.

Michael Schiff, M.D.
Denver Arthritis Clinic

Date

Kenneth J. Gorelick, M.D.
Vice President,
Medical and Regulatory Affairs
Genelabs Incorporated

Date

Protocol #GL 94-01

SUMMARY OF AMENDMENTS

1. Amendment #1- 4/25/94

Adds measurements of bone mass using dual photon absorptiometry at the Qualifying and Completion visits at one site (Denver Arthritis Clinic).

AMENDMENT #1

The purpose of the amendment is to examine the effects of DHEA on bone mass when administered to patients with mild to moderate lupus. Many patients with mild to moderate lupus receive glucocorticoids. One of the severe toxicities associated with chronic administration of glucocorticoids is osteoporosis. In animal studies, DHEA was reported to promote bone growth and ameliorate the sequelae of osteoporosis due to ovariectomy. Therefore, it will be important to examine the effects of DHEA on bone mass in this study. Bone mass will be measured using dual photon absorptiometry at the Qualifying and Completion Visits. This procedure will be added for patients enrolled at Denver Arthritis Clinic only. Comparisons of baseline and completion absorptiometry values will indicate whether the repeat administration of DHEA (GL701) has any effect on bone mass.

Therefore, the following changes will be made to the protocol.

1. Section 6.2, Qualifying Visit: page 17.

Addition:

6.2.9 Measurement of bone mass using dual photon absorptiometry.

2. Section 6.5, Completion or Termination Visit: page 18.

Addition:

6.5.7 Measurement of bone mass using dual photon absorptiometry.

3. Appendix 11.4, Schedule of Events: page 38.

Addition:

Under Required Tests, measurement of bone mass using dual photon absorptiometry at Qualifying and Completion / Termination visits is indicated. (see attached).

Protocol #GL94-01
March 14, 1994

Amendment #2
July 29, 1994

A Double-Blind, Randomized Phase II/III Study of GL701 in Female Patients with Mild to Moderate Systemic Lupus Erythematosus

I have received and read the Investigational Drug Brochure for GL701 dated 12/93, the protocol dated 3/14/94, the amendment dated 7/29/94, and the Statement of Investigator Obligations. I agree to undertake the study as defined therein. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved by Genelabs Technologies, Inc. and the Institutional Review Board. Failure to adhere to those stipulations may constitute a breach of federal regulations and may result in termination of the study.

Investigator
Site

Date

Kenneth J. Gorelick, M.D.
Vice President,
Medical and Regulatory Affairs
Genelabs Incorporated

Date

Protocol #GL 94-01

SUMMARY OF AMENDMENTS

1. Amendment #1- 4/25/94

Adds measurements of bone mass using dual photon absorptiometry at the Qualifying and Completion visits at one site (Denver Arthritis Clinic).

2. Amendment #2- 7/29/94

Changes the requirement for lab specimen collection to the day of the study visits instead of within 10 days prior to study visits. SLEDAI score calculations will be done as the lab results are reported, and subsequent required changes in prednisone dose levels will be telephoned to the patient within a required time frame. All patients who have a $\geq 2+$ level of urine protein by the urinalysis dipstick at any visit will be required to take a 24 hour urine collection for quantitative urine protein. A long term follow up visits will be required of those patients who complete GL94-01 but who do not enroll in any of the follow up studies. Follow up phone contact will be required for those patients who discontinue study treatment prematurely. Clarifications are made regarding laboratory testing, English language requirements, study medication storage, prednisone use, NSAID use and unblinding procedures.

AMENDMENT #2

The purpose of the amendment is to decrease the number of visits required of the patients by eliminating separate visits for laboratory specimen collection, to change urine protein testing requirements to a more appropriate method for the SLEDAI score, to formalize follow up procedures for all patients enrolled in the study, and to clarify laboratory testing, study medication storage, english requirements for study entry, prednisone use, NSAID use and unblinding notification.

Patients will now be required to visit the study site on a monthly basis after the Qualifying Visit. Specimen collections for laboratory evaluations will now occur on the day of the study visits instead of within 10 days prior to study visits. SLEDAI score calculations will be done as the lab results are reported, and subsequent required changes in prednisone dose levels must be telephoned to the patient as soon as possible but not longer than 5 working days after the study visit.

In addition to the required 24 hour urine collection at Screening and Completion / Termination Visits, all patients who have a $\geq 2+$ level of urine protein by the urinalysis dipstick method at any of the other study visits will be required to take a 24 hour urine collection as soon as possible for quantitative urine protein analysis. Again, SLEDAI score calculations will be done as the lab results are reported, and subsequent required changes in prednisone dose levels must be telephoned to the patient as soon as possible but not longer than 5 working days after the study visit.

A follow up visit at 12 months after study entry will be required for those patients who complete GL94-01 but who do not enroll in any of the Genelabs' sponsored follow up studies. Those patients who discontinue from GL94-01 prematurely will be telephoned at 12 months after study entry for a brief review of health status including adverse events.

All patients who enter the study must have a command of the English language that will allow them to complete the self-administered surveys.

Special storage conditions for study medication are necessary in high heat and humidity.

The lipid panel (Total serum cholesterol, LDL, HDL and triglycerides) is performed at Screening and Completion / Termination visits only.

In the event of an unblinding of treatment code, notify Randi McFarland (Associate Director of Clinical Data Management) or her backup at Genelabs of unblinding of treatment code.

NSAIDs may be taken on a prn basis as long as the average dose remains constant.

Prednisone (or equivalent glucocorticoid) may be taken in divided daily doses (BID, TID, etc.) if clinically indicated.

Changes to the protocol are as follows:

ADDITION TO SECTION 4.2:

- 4.2.14 All patients must have a basic command of the English language in order to complete the self-administered surveys (10 cm Visual Analog Scale and assessments of health status and fatigue).

SECTION 5.1.2 ORIGINALLY READS:

- 5.1.2 Drug Supply: Study medication will be supplied in hard, gelatin capsules. Each capsule contains either 50 mg DHEA or placebo. Four capsules of study medication are to be taken each morning. Study medication is to be stored at room temperature, 59-86°F in a dry place.

Changed text:

- 5.1.2 Drug Supply: Study medication will be supplied in hard, gelatin capsules. Each capsule contains either 50 mg DHEA or placebo. All four capsules of study medication are to be taken each morning. Study medication is to be stored at room temperature, 59-86°F in a dry place. **Special storage conditions will be required for high heat and humidity. (Consult with Genelabs if necessary.)**

SECTION 5.1.5 ORIGINALLY READS:

- 5.1.5 Each monthly envelope will contain a double-blind label specifying the study number, patient number, and directions for use. This double-blind label will have a portion permanently affixed to the envelope, and a tear off portion to keep in the pharmacy. In the event of an emergency that requires the unblinding of a patient's treatment code, the covered section of the tear off portion of the label can be swabbed with alcohol to reveal the treatment code of the patient and the lot number of the medication. Genelabs and the Independent Monitoring Board should be notified immediately if any patient is unblinded and unblinding should be noted in the case report form.

Changed text:

- 5.1.5 Each monthly envelope will contain a double-blind label specifying the study number, patient number, and directions for use. This double-blind label will have a portion permanently affixed to the envelope, and a tear off portion to keep **with drug accountability records**. In the event of an emergency that requires the unblinding of a patient's treatment code, the covered section of the tear off portion of the label can be swabbed with alcohol to reveal the treatment code of the patient and the lot number of the medication. **Randi McFarland (Associate Director of Clinical Data Management, 415-369-9500, extension 264)**

or her backup at Genelabs should be notified immediately if any patient is unblinded.

ADDITION TO SECTION 5.2:

5.2.3 SLEDAI score will be completed when laboratory results are reported to the site. In the event that a patient demonstrates a $\geq 2+$ result in urine protein by dipstick method, the central lab will alert you by telephone. The patient must immediately have a 24 hour urine collection for urine protein quantification if it has not already been collected as required at the Screening and Completion / Termination Visits. The SLEDAI may then be completed when the urine protein quantification results are received. When appropriate (see Study Activities, section 6), the patient must be notified as soon as possible but no longer than 5 working days after the study visit of any required changes in prednisone dose. The recommended dose and date of patient contact must be indicated on the Medication Record case report form for that visit, and actual date on which the patient implemented the change in dose must be recorded on the Glucocorticoid Medication case report form.

5.2.4 Prednisone may be taken in divided daily doses (BID, TID etc.) if clinically indicated.

SECTION 5.3.4 ORIGINALLY READS:

5.3.4 No changes from baseline (study entry) are allowed for dosages of Plaquenil (hydroxychloroquine) or NSAIDs except for documented drug toxicity.

Changed text:

5.3.4 No changes from baseline (study entry) are allowed for dosages of Plaquenil (hydroxychloroquine) or NSAIDs except for documented drug toxicity. **NSAIDs may be taken on a prn basis as long as the average dose remains consistent throughout the course of the study.**

SECTION 6.2.8 ORIGINALLY READS:

6.2.8 Schedule patient for laboratory evaluations not more than 10 days prior to Visit 1- (Week 4).

Changed text:

- 6.2.8 Schedule patient for Visit 1- (Week 4) to include specimen collection for laboratory evaluations.

SECTION 6.3.4 ORIGINALLY READS:

- 6.3.4 Disease Assessment as in 6.2.4 to 6.2.6.

Changed text:

- 6.3.4 Disease Assessment as in 6.2.4 to 6.2.6. **SLEDAI score (Disease Assessment 6.2.4) will be completed when laboratory results are reported to the site. In the event that a patient demonstrates a $\geq 2+$ result in urine protein by dipstick method, the central lab will alert you by telephone. The patient must immediately have a 24 hour urine collection for urine protein quantification. The SLEDAI may then be completed when the urine protein quantification results are received. The patient must be notified as soon as possible but no longer than 5 working days after the study visit of any required changes in prednisone dose. The recommended dose and date of patient contact must be indicated on the Medication Record case report form for that visit, and actual date on which the patient implemented the change in dose should be recorded on the Glucocorticoid Medication case report form.**

SECTION 6.3.5 ORIGINALLY READS:

- 6.3.5 Laboratory evaluations as in 6.1.7 to 6.1.11, 6.1.17.

Changed text:

- 6.3.5 Laboratory evaluations as in 6.1.7 to 6.1.11, 6.1.17 **excluding total serum cholesterol, LDL, HDL and triglycerides. Laboratory specimens are collected on the day of the Dosing Visit, and results are reported to the site except for pharmacokinetic results which will remain blinded to the site. In the event that a patient demonstrates a $\geq 2+$ result in urine protein by dipstick method, the central lab will alert you by telephone, and the patient must immediately have a 24 hour urine collection for urine protein quantification.**

SECTION 6.3.7 ORIGINALLY READS:

- 6.3.7 Schedule patient for laboratory evaluations not more than 10 days prior to Visit 2-Week 8.

Changed text:

- 6.3.7 Schedule patient for Visit 2- Week 8 to include specimen collection for laboratory evaluations.

SECTION 6.4 ORIGINALLY READS:

- 6.4 Dosing Visits 2 through 6 - Weeks 8, 12, 16, 20, 24 and in the event of delayed reduction in prednisone (see section 4.5), Dosing Visits 7 and 8 (Weeks 28 and 32)

Same as section 6.3 excluding lab 6.1.17.

- 6.4.1 Reminder: Schedule patient for laboratory evaluations not more than 10 days prior to each visit. Patients should take their study medication after laboratory specimens are drawn.

Changed text:

- 6.4 Dosing Visits 2 through 6 - Weeks 8, 12, 16, 20, 24 and in the event of delayed reduction in prednisone (see section 4.5), Dosing Visits 7 and 8 (Weeks 28 and 32)

Same as section 6.3 excluding lab 6.1.17

Section 6.4.1 is deleted.

SECTION 6.5.1 ORIGINALLY READS:

- 6.5.1 Labs: Same as 6.1.7 to 6.1.17. Patients should be fasting for at least 8 hours before specimens are drawn.

Changed text:

- 6.5.1 Labs: Same as 6.1.7 to 6.1.17. Patients should be fasting for at least 8 hours before specimens are drawn. **Laboratory specimens are collected on the day of the Completion / Termination Visit, and results are reported to the site except for pharmacokinetic results which will remain blinded to the site.**

SECTION 6.5.2 ORIGINALLY READS:

6.5.2 Disease activity assessments: 6.1.6 and 6.2.4 to 6.2.6.

Changed text:

6.5.2 Disease activity assessments: 6.1.6 and 6.2.4 to 6.2.6. **SLEDAI score (Disease Assessment 6.2.4) will be completed when laboratory results are reported to the site. The recommended dose of prednisone must be indicated on the Medication Record case report form for that visit.**

SECTION 6.6 ORIGINALLY READS:**6.6 Follow up for All Patients**

All patients are encouraged to undergo follow up as below.

- 6.6.1 Patients who complete study GL94-01 according to protocol will be eligible for dosing in a subsequent study.
- 6.6.2 Patients who complete study GL94-01 according to protocol and who do not wish to continue to receive GL701 will be asked to return for a follow up evaluation visit 12 months after the Qualifying Visit.
- 6.6.3 Patients who withdraw from the study for any reason will be asked to return for follow up evaluation visits at 7 months and 12 months after the Qualifying Visit.

Changed text:**6.6 Follow up for All Patients**

- 6.6.1 Patients who complete study GL94-01 according to protocol will be eligible for dosing in a subsequent study.
- 6.6.2 Patients who complete study GL94-01 according to protocol and who do not wish to continue to receive GL701 or who do not qualify for a subsequent study will be asked to return for a follow up evaluation visit 12 months after the Qualifying Visit. **Follow up evaluations include all study activities in section 6.5 including laboratory evaluations.**
- 6.6.3 Patients who prematurely withdraw from the study for any reason will be **telephoned at 12 months after the Qualifying Visit to review any adverse events that were ongoing at study completion.**

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PART OF SECTION 8.3 ORIGINALLY READS:

The GL701 drug supply will be packaged in a blinded manner and shipped from Simirex to the sites. Only authorized personnel designated by the Principal Investigator should have access to the drug. Study medication should be stored at room temperature (59-86°F) in a dry place.

Changed Text:

The GL701 drug supply will be packaged in a blinded manner and shipped from Simirex to the sites. Only authorized personnel designated by the Principal Investigator should have access to the drug. Study medication should be stored at room temperature (59-86°F) in a dry place. **Special storage conditions will be required for high heat and humidity. (Consult with Genelabs if necessary.)**

Protocol #GL94-01
March 14, 1994

Amendment #3
November 10, 1994

**A Double-Blind, Randomized Phase II/III Study of GL701 in Female
Patients with Mild to Moderate Systemic Lupus Erythematosus**

I have received and read the Investigational Drug Brochure for GL701 dated 12/93, the protocol dated 3/14/94, the amendment dated 11/10/94, and the Statement of Investigator Obligations. I agree to undertake the study as defined therein. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved by Genelabs Technologies, Inc. and the Institutional Review Board. Failure to adhere to those stipulations may constitute a breach of federal regulations and may result in termination of the study.

Michelle Petri, M.D.
Johns Hopkins

Date

Kenneth J. Gorelick, M.D.
Vice President,
Medical and Regulatory Affairs
Genelabs Incorporated

Date

Protocol #GL 94-01

SUMMARY OF AMENDMENTS

1. Amendment #1- 4/25/94

Adds measurements of bone mass using dual photon absorptiometry at the Qualifying and Completion visits at one site (Denver Arthritis Clinic).

2. Amendment #2- 7/29/94

Changes the requirement for lab specimen collection to the day of the study visits instead of within 10 days prior to study visits. SLEDAI score calculations will be done as the lab results are reported, and subsequent required changes in prednisone dose levels will be telephoned to the patient within a required time frame. All patients who have a $\geq 2+$ level of urine protein by the urinalysis dipstick at any visit will be required to take a 24 hour urine collection for quantitative urine protein. A long term follow-up visit will be required of those patients who complete GL94-01, but who do not enroll in any of the follow-up studies. Follow-up phone contact will be required for those patients who discontinue study treatment prematurely. Clarifications are made regarding laboratory testing, English language requirements, study medication storage, prednisone use, NSAID use and unblinding procedures.

3. Amendment #3-11/10/94 (Selected Sites)

Adds two (2) timepoints for the collection of serum samples for plasma levels of DHEA-S at selected sites. Specimens for DHEA-S will now be drawn at Screening, Dosing Visits 1,2, and 3, and Completion or Termination visits to be assayed and banked by the Genelabs Quality Control Department.

AMENDMENT #3

The purpose of this amendment is to increase the number of serum specimens collected for the determination of plasma levels of DHEA-S from 3 to 5 at selected sites. The timepoints will now include Screening, Dosing Visits 1,2,3 and Completion or Termination Visits. These specimens will be drawn the day of the designated visits. Patients should take their study medication after the laboratory specimens are drawn.

Section 6.4, 6.4.1, page 18**Previously written to state:**

- 6.4 Dosing Visits 2 through 6 - Weeks 8,12, 16, 20, 24 and in the event of delayed reduction of prednisone (see section 4.5), Dosing Visits 7 and 8 (weeks 28 and 32).

Same as Section 6.3 excluding lab 6.1.17.

- 6.4.1 Reminder: Schedule patient for laboratory evaluations not more than 10 days prior to each visit. Patients should take their study medication after laboratory specimens are drawn.

Re-written to state:

- 6.4 Dosing Visits 2 through 6 - Weeks 8,12, 16, 20, 24 and in the event of delayed reduction of prednisone (see section 4.5), Dosing Visits 7 and 8 (weeks 28 and 32).

Dosing Visits 2 and 3 - Same as 6.3 (including serum samples for DHEA-S levels).

Dosing Visits 4 through 6 (7 and 8, see Section 4.5)- Same as 6.3 (excluding serum samples for DHEA-S levels).

- 6.4.1 Reminder: Schedule patient for laboratory evaluations the *day of visit*. Patients should take their study medication after laboratory specimens are drawn.

Schedule of Events, Section 11.4, page 38**Addition of:**

Serum samples for DHEA-S pharmacokinetics evaluation at *Dosing Visits 2 and 3*.

Amendment to Investigator Reference Manual

November 10, 1994

Appendix A, Section I, page 35: Procedures for Processing and Shipping GL701 Pharmacokinetics Specimens for Study GL94-01.

Previously written to state:

- I. This procedure applies to the specimen collection for serum DHEA-SULFATE levels for pharmacokinetics evaluation. Specimens are taken at Screening, Dosing 1 and Completion or Termination visits, and are assayed and banked by the Genelabs Quality Control Department.

Re-written to state:

- I. This procedure applies to the specimen collection for serum DHEA-SULFATE levels for pharmacokinetics evaluation. Specimens are taken at Screening, Dosing 1, 2, *and* 3 and Completion or Termination visits, and are assayed and banked by the Genelabs Quality Control Department.

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AMENDMENT #4

The purpose of this amendment is to revise the procedures for the return of study medication and the statistical section.

PREVIOUSLY WRITTEN TO STATE:

All packaging and partially used and unused drug supplies will be returned to Simirex. Return of all drug supplies must be coordinated with the CRA prior to shipment. When either used or unused drug supplies are to be returned, the Pharmacist should record the number of used and/or unused blister packs and lot numbers being returned on the Drug Inventory Sheet, and complete the Return of Clinical Investigational Material form provided by the CRA.

Upon completion of this study, the Investigator and Pharmacist should verify and sign that all drug supplies, including all used blister packs, have been returned for each study subject and that no drug supplies remain in the Investigator's possession. If all drug supplies are not returned, the Investigator must include an explanation and document all attempts to have the supplies returned. A copy of the Drug Inventory Sheets will be collected by the CRA.

Return Used and Unused Blister Packs To:

Simirex Inc.
12000C Commerce Parkway
Mount Laurel, NJ 08054

REWRITTEN TO STATE:

All packaging and partially used and unused drug supplies will be returned to Genelabs. Return of all drug supplies must be coordinated with the CRA prior to shipment. When either used or unused drug supplies are to be returned, the Pharmacist should record the number of used and/or unused blister packs and lot numbers being returned on the Drug Inventory Sheet, and complete the Return of Clinical Investigational Material form provided by the CRA.

Upon completion of this study, the Investigator and Pharmacist should verify and sign that all drug supplies, including all used blister packs, have been returned for each study subject and that no drug supplies remain in the Investigator's possession. If all drug supplies are not returned, the Investigator must include an explanation and document all attempts to have the supplies returned. A copy of the Drug Inventory Sheets will be collected by the CRA.

Return Used and Unused Blister Packs To:

Stacie Chen
Clinical Assistant
Genelabs Technologies, Inc.
505 Penobscot Drive
Redwood City, CA 94063

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PREVIOUSLY WRITTEN TO STATE:

9. STUDY ANALYSIS

9.1 Baseline Comparability

Baseline values, including demographic variables and disease status, will be compared between the treatment groups by summary tables and by Cochran-Mantel-Haenszel test or ANOVA with stratification by or control for site. Variables attaining statistical significance levels less than 0.05 for association with treatment assignment may be included as covariables or stratifying variables in analysis.

The baseline value for all variables will be the last value measured or obtained prior to initiation of study treatment. Age is age on the day of first study treatment.

9.2 Blinding

Patients, investigators, all persons involved in running the study, and all employees of the sponsor except for a designated statistician are blinded to patient treatment assignments. No unblinding will take place until after all patients in the study have completed the blinded portion of the study and all data from the blinded portion of the study have completed all data verification and all data query resolution, including all classification of treatment terminations and resolution of data query issues surfaced during test runs of analysis programs.

Both patients and investigators will be asked at study termination to guess which treatment arm the patient was in. These results will be displayed and their possible affect upon study results will be assessed. The function of this analysis is to assess the degree to which differing side effect profiles could affect the double blind. If the treatment efficacy is so strong that patients or investigators can infer treatment from efficacy results then an association between actual treatment and guessed treatment is expected to occur.

All decisions regarding admissibility of data for any patient for analysis will be made prior to the unblinding to anyone of the treatment assignment for that patient. Since data questions may surface during analysis, this requires maintenance of the blind until final analysis programs have been tested on the group as a whole. Reasons for all data exclusions will be documented. Any data exclusion which has to be made after unblinding will be noted and explained and its impact on the results will be evaluated.

9.3 Efficacy

9.3.1 Patient Evaluability for Efficacy Analysis

Patients who terminate treatment prior to completing four months will be excluded from the primary analyses. These patients will be included in an intent-to-treat analysis only. Both the primary analyses and the intent-to-treat analyses will be terminal visit analyses. Reasons for

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any exclusions from any analysis will be thoroughly documented.

9.3.2 Primary Efficacy Variables

This study includes two primary efficacy variables. The two variables are

1. Achievement of a sustained decrease in prednisone dose to 7.5 mg/day or less, and this decrease must be sustained for no less than two months, and
2. Percent decrease in prednisone use, comparing final dose with baseline.

The first primary efficacy variable assesses clinically important reduction in daily prednisone use. This variable is specifically designed to reflect treatment's ability to provide benefit consistent with 21 CFR 312 Subpart E status.

The second primary efficacy variable assesses percent reduction achieved in daily prednisone use. This variable has been agreed upon by a panel of experts in the treatment of SLE to be the best single variable quantitative assessment of treatment benefit.

Reductions in prednisone use are expected to be without meaningful increase in SLEDAI because of the prednisone dose tapering rules, however this assumption will also be checked by secondary analysis.

Analysis of primary efficacy variable 1 will be by logistic regression analysis of the proportion achieving success controlling for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

Analysis of primary efficacy variable 2 will be by ANOVA with control for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

As noted above, all decisions regarding admissibility of data for analysis will be made prior to unblinding. Differences between the treatment groups in the distribution of early terminations, should such differences occur, will be assessed for possible effect on the primary outcome analyses. Intent-to-treat analyses will also be made. Differences between primary analyses and intent-to-treat analyses, should they occur, will be assessed regarding the generalizability of results. Tests will be two sided at alpha level .05.

9.3.3 Secondary Efficacy Variables

Secondary efficacy variables include

- 1) Time to increase in SLEDAI score
- 2) Change in SLEDAI
- 3) Change in quality of life assessment
- 4) Improvement in global assessment of disease activity utilizing a 10cm VAS scale by

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physician.

- 5) Improvement in global assessment of disease activity utilizing a 10cm VAS scale by patient assessment of disease severity
- 6) Improvement in body mass index
- 7) Improvement in lipid profile
- 8) Quantitative changes in renal function
- 9) Quantitative changes in hematologic function

Results will be displayed and analyzed if appropriate.

9.3.4 Power

Initial sample size is 190 patients randomized to treatment. Power calculations are performed for a sample size of 168, 56 in each arm. The difference of 22 approximately compensates for loss in power from having to control for site and from early withdrawals.

With respect to primary efficacy variable 1: a sample size of 56 evaluable patients in each arm gives a power of approximately 80% for the pair-wise two-sided tests of primary efficacy variable 1 at $\alpha=.05$ if the true probability of success on one treatment is .05 and the true probability of success on the other treatment is .22. The power is also 80% if the true probabilities are .10 and .30 or .20 and .44. The power is approximately 50% if the true probabilities of success are .05 and .16 or .10 and .24 or .20 and .37, respectively.

With respect to primary efficacy variable 2: A sample size of 56 patients in each arm gives a power of 80% for the pair-wise two-sided tests of primary efficacy variable 2 at $\alpha=.05$ if the true difference between the two treatments is 30 and the true within group between-patient standard deviation is 55.

The assumption that the true within group between-patient standard deviation is 55 is temporary until the limited interim analysis gives an estimate. Sample size will then be adjusted to ensure 80% power for a treatment effect of 30.

9.4 Safety

Changes in lab values and incidence of adverse events by treatment group will be displayed by descriptive statistics. If appropriate, differences between treatment groups will be compared by Cochran-Mantel-Haenszel test or by ANOVA of ranks or by Spearman rank correlation.

9.5 Interim analysis

A limited interim analysis will be performed in order to adjust the sample size to ensure adequate power for primary efficacy variable 2. The limited interim analysis will be carried out under the control of an independent study monitoring board and no information regarding interim treatment efficacy differences will be issued or used in the sample size adjustment. In particular, no information regarding interim treatment differences will be released to anyone who is blinded to patient assignments.

The limited interim analysis study will provide an interim (pooled) estimate of the patient to patient variability within treatment groups for primary efficacy variable 2. The limited interim analysis will be scheduled for all evaluable data available for analysis on the date of the four month anniversary of the enrollment of the 95th patient. If results for at least 50 evaluable patients are not available at that time then the interim will be performed once results for 50 evaluable patients are available. Results regarding pooled within group between-patient variation in primary efficacy variable 2 will be used to adjust the sample size.

9.6 Sample Size Adjustment

The sample size will be adjusted to ensure adequate power to detect treatment effects upon primary efficacy variable 2.

The interim estimate of between-patient variability will be used to calculate the number of patients needed to give 80% power for the two-sided test at $\alpha=0.05$ if the true treatment effect on primary efficacy variable 2 is 30, i.e. if the true expected treatment induced percent reduction is greater by 30 than the true placebo value. If the re-estimated sample size estimate is less than 168 then the study will continue as planned, no reduction in sample size will occur. If the re-estimated sample size is greater than 168, then the sample size for the study will be increased accordingly in order to ensure an adequately powered study. All valid data from the study will be used in the final analyses; this is not the type of two stage design which eliminates some of the interim data from use in the final analysis.

The use of interim pooled between-patient variability results to adjust total sample size gives a type of two stage study design. Use of all study data in the final analysis of a two stage study maximizes power but may require an adjustment in the final significance level. Procedures for appropriate adjustment of the nominal final alpha will be developed and submitted by the sponsor for approval by the FDA statistician prior to the interim analysis.

9.7 Independent Study Monitoring Board

An independent study monitoring board (ISMB) will be created. The ISMB will perform the following functions:

1. Confidentially monitor key safety parameters for indications that the study should be terminated because of safety considerations.
2. Monitor the generation and confidentiality of the limited interim analysis used to re-estimate sample size.
3. Monitor and provide guidance on any issue related to patient's welfare and the validity of the study, including amendments to the protocol.

The ISMB will include appropriate medical and statistical expertise. ISMB members must be free from conflicts of interest. The ISMB will receive its information from the designated statistician who also performs the confidential limited interim analysis.

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REWRITTEN TO STATE:

9. STUDY ANALYSIS

9.1 Baseline comparability

Baseline values, including demographic variables and efficacy variables, will be compared among the treatment groups by Cochran-Mantel-Haenszel test or one-way ANOVA with treatment as factor. Variables attaining statistical significance at the level of 0.05 will be included in the primary efficacy analyses to examine the effect of the imbalance of such variables among the treatment groups.

The baseline value for all variables will be the last value measured or obtained prior to initiation of study treatment. Age is age on the day of first study treatment.

9.2 Blinding

Patients, investigators, all persons involved in running the study, and all employees of the sponsor except for a designated statistician are blinded to patient treatment assignments. No unblinding will take place until after all patients in the study have completed the blinded portion of the study and all data from the blinded portion of the study have completed all data verification and all data query resolution.

All decisions regarding admissibility of data for any patient for analysis and sub-group analysis will be made prior to the unblinding to anyone of the treatment assignment for that patient. Since data questions may surface during analysis, this requires maintenance of the blind until all data verification and all data query resolution are completed. Reasons for all data exclusions will be documented. Any data exclusion which has to be made after unblinding will be noted and explained and its impact on the results will be evaluated.

9.3 Efficacy

All statistical tests performed will be two-sided, and a level of 0.05 will be used to declare statistical significance.

9.3.1 Patient Evaluability for Efficacy Analysis

All analyses will be performed as intent-to-treat analyses at Dosing Visit 6 except the intent-to-treat analysis for the first primary efficacy variable. For each efficacy variable, the intent-to-treat analysis at Dosing Visit 6 will only include the randomized patients who had baseline measurement and at least one post-baseline measurement on or before Dosing Visit 6. The last measurement on or before Dosing Visit 6 will be analyzed.

9.3.2 Primary Efficacy Variables

This study includes two primary efficacy variables. The two variables are

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1. Achievement of a sustained decrease in prednisone dose to 7.5 mg/day or less, and this decrease must be sustained for no less than two months, and
2. Percent decrease in prednisone use, comparing final dose with baseline.

The first primary efficacy variable assesses clinically important reduction in daily prednisone use. This variable is specifically designed to reflect treatment's ability to provide benefit consistent with 21 CFR 312 Subpart E status.

The second primary efficacy variable assesses percent reduction achieved in daily prednisone use. This variable has been agreed upon by a panel of experts in the treatment of SLE to be the best single variable quantitative assessment of treatment benefit.

Only the prednisone dose recorded in the medication record form will be used for these two primary efficacy variables.

Reductions in prednisone use are expected to be without meaningful increase in SLEDAI because of the prednisone dose tapering rules, however this assumption will also be checked by secondary analysis.

Analysis of primary efficacy variable 1 will be by logistic regression analysis of the proportion achieving success controlling for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

Analysis of primary efficacy variable 2 will be by ANOVA with control for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

If there is a study site with fewer than 3 intent-to-treat patients in one treatment group, then this study site's data will be pooled. The step-by-step iterative pooling scheme is described in the following:

- Step 1. Among the group of study sites for which pooling is required (fewer than 3 patients), the study site with the smallest total number of intent-to-treat patients will be selected. This study site and the study site with next smallest total number of intent-to-treat patients among this group will be pooled together and identified as a new study site.
- Step 2. After creation of the new study site described in step 1, all study sites, including the newly created one, with fewer than 3 intent-to-treat patients in one treatment group will be selected. If there are more than two such study sites, then step 1 will be repeated in an

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iterative manner. If there is no such study site, then no additional pooling will be done.

If there is only one such (fewer than 3 intent-to-treat patients in one treatment group) study site, then this study site and the study site, with the smallest total number of intent-to-treat patients among the remaining study sites, will be pooled together.

The descriptive statistics for the primary efficacy variables by treatment group will be displayed.

9.3.3 Secondary Efficacy Variables

Secondary efficacy variables include

- 1) Change from baseline in SLEDAI
- 2) Change from baseline in quality of life assessment by SF-36
- 3) Change from baseline in Krupp Fatigue Score
- 4) Change from baseline in global assessment of disease activity by physician
- 5) Change from baseline in global assessment of disease activity by patient

All secondary efficacy variables will be analyzed by means of a two-way analysis of covariance model with treatment and trial center as factors and baseline (Qualifying Visit) as a covariate. Both treatment-by-baseline and treatment-by-center interactions will be included in the model.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

If there is a study site with fewer than 3 intent-to-treat patients in one treatment group, then this study site's data will be pooled by the pooling scheme described in 9.3.2.

The summary statistics for these efficacy variables by treatment group will be displayed.

9.4 Safety

Changes in laboratory values and incidence of adverse events by treatment group will be displayed by descriptive statistics. The three-treatment-group comparison will be performed by either Cochran-Mantel-Haenszel test or one-way ANOVA.

9.5 Interim analysis

A limited interim analysis will be performed in order to adjust the sample size to ensure adequate power for primary efficacy variable 2. The limited interim analysis will be carried out under the control of an independent study monitoring board and no information regarding interim treatment efficacy differences will be issued or used in the sample size adjustment. In particular, no information regarding interim treatment differences will be released to anyone who is blinded to

patient assignments.

The limited interim analysis will provide an interim (pooled) estimate of the patient to patient variability within treatment groups for primary efficacy variable 2. This information will be used for adjusting the sample size of the study. The limited interim analysis will be scheduled for the date that the data are complete for the first 60 evaluable patients (the order of evaluable patients will be ranked by the date of randomization). An evaluable patient is defined as one for whom both baseline measurement and at least one post-baseline measurement in prednisone dose have been recorded. Only the prednisone dose data for these 60 patients will be used for interim analysis.

9.6 Sample Size Determination

Initial sample size is 190 randomized patients to allow 168 patients to complete the study. The sample size will be adjusted to ensure adequate power to detect treatment effects upon primary efficacy variable 2.

The intent-to-treat analyses at Dosing Visit 6 for the primary efficacy variable 2 will be conducted for the interim analysis by means of a one-way analysis of variance with treatment group as factor. The mean squared error from this analysis will be used as an interim estimate of between-patient variance. The sample size will be recalculated to give 80% power for the two-sided pairwise comparison at the level of 0.025 (due to the Bonferroni's adjustment) if the true treatment difference from placebo in primary efficacy variable 2 is 30%. If the re-estimated sample size for all three treatment group is less than 168 then the study will continue as planned; no reduction in sample size will occur. If the re-estimated sample size is greater than 168, then the sample size for the study will be increased accordingly to allow the observed dropout rate from the 60 patients in the interim analysis and ensure an adequately powered study.

In order to blind all the results except between-patient variability from the interim analysis, the interim analysis will be analyzed by a statistician who is not the project statistician. Only the between-patient variability will be released for sample size recalculation.

Since no relative efficacy results will be available at the interim stage, this interim analysis is an administrative interim analysis. Wittes and Brittain (1990) and Gould and Shih (1992) have shown that the procedure of sample size reestimation inflates the Type I error rate only very minimally (about the order of 10^{-3}), but the gain in maintaining the power can be very substantial. So, no adjustment of Type I error will be made for this study.

9.7 Independent Study Monitoring Board

An independent study monitoring board (ISMB) will be created. The ISMB will perform the following functions:

1. Confidentially monitor key safety parameters for indications that the study should be terminated because of safety considerations.
2. Monitor the generation and confidentiality of the limited interim analysis used to re-

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estimate sample size.

3. Monitor and provide guidance on any issue related to patient's welfare and the validity of the study, including amendments to the protocol.

The ISMB will include appropriate medical and statistical expertise. ISMB members must be free from conflicts of interest. The ISMB will receive its information from the designated statistician who also performs the confidential limited interim analysis.

References

Wittes J, Brittain E. (1990) The role of internal pilot studies in increasing the efficacy of clinical trials. *Statistics in Medicine*, 9, 65-72.

Gould AL, Shih WJ. (1992) Sample size reestimation without unblinding for normally distributed outcomes with unknown variance. *Communication in Statistics (A)*, 21(10), 2833-2853.

GL701 (DHEA for SLE)
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1/18/95 (rev. 07/18/95)
Abridged and Revised

AMENDMENT #4

The purpose of this amendment is to revise the procedures for the return of study medication and the statistical section. Please note that the following text is an abridgement of the actual amendment, which has been edited to remove the "previously written" protocol text, since the original protocol is contained herein. The amendment makes the following changes:

SECTION 8.3 (DRUG ACCOUNTABILITY) PARAGRAPHS 4, 5 AND 6 IS REWRITTEN TO STATE:

All packaging and partially used and unused drug supplies will be returned to Genelabs. Return of all drug supplies must be coordinated with the CRA prior to shipment. When either used or unused drug supplies are to be returned, the Pharmacist should record the number of used and/or unused blister packs and lot numbers being returned on the Drug Inventory Sheet, and complete the Return of Clinical Investigational Material form provided by the CRA.

Upon completion of this study, the Investigator and Pharmacist should verify and sign that all drug supplies, including all used blister packs, have been returned for each study subject and that no drug supplies remain in the Investigator's possession. If all drug supplies are not returned, the Investigator must include an explanation and document all attempts to have the supplies returned. A copy of the Drug Inventory Sheets will be collected by the CRA.

Return Used and Unused Blister Packs To:

Stacie Chen
Clinical Assistant
Genelabs Technologies, Inc.
505 Penobscot Drive
Redwood City, CA 94063

SECTION 9 (STUDY ANALYSIS) IS REWRITTEN TO STATE:

9.1 Baseline comparability

Baseline values, including demographic variables and efficacy variables, will be compared among the treatment groups by Cochran-Mantel-Haenszel test or one-way ANOVA with treatment as factor. Variables attaining statistical significance at the level of 0.05 will be included in the primary efficacy analyses to examine the effect of the imbalance of such variables among the treatment groups.

The baseline value for all variables will be the last value measured or obtained prior to initiation of study treatment. Age is age on the day of first study treatment.

9.2 Blinding

Patients, investigators, all persons involved in running the study, and all employees of the sponsor except for a designated statistician are blinded to patient treatment assignments. No unblinding will take place until after all patients in the study have completed the blinded portion of the study and all data from the blinded portion of the study have completed all data verification and all data query resolution.

All decisions regarding admissibility of data for any patient for analysis and sub-group analysis will be made prior to the unblinding to anyone of the treatment assignment for that patient. Since data questions may surface during analysis, this requires maintenance of the blind until all data verification and all data query resolution are completed. Reasons for all data exclusions will be documented. Any data exclusion which has to be made after unblinding will be noted and explained and its impact on the results will be evaluated.

9.3 Efficacy

All statistical tests performed will be two-sided, and a level of 0.05 will be used to declare statistical significance.

9.3.1 Patient Evaluability for Efficacy Analysis

All analyses will be performed as intent-to-treat analyses at Dosing Visit 6 except the intent-to-treat analysis for the first primary efficacy variable. For each efficacy variable, the intent-to-treat analysis at Dosing Visit 6 will only include the randomized patients who had baseline measurement and at least one post-baseline measurement on or before Dosing Visit 6. The last measurement on or before Dosing Visit 6 will be analyzed.

9.3.2 Primary Efficacy Variables

This study includes two primary efficacy variables. The two variables are

1. Achievement of a sustained decrease in prednisone dose to 7.5 mg/day or less, and this decrease must be sustained for no less than two months, and
2. Percent decrease in prednisone use, comparing final dose with baseline.

The first primary efficacy variable assesses clinically important reduction in daily prednisone use. This variable is specifically designed to reflect treatment's ability to provide benefit consistent with 21 CFR 312 Subpart E status.

The second primary efficacy variable assesses percent reduction achieved in daily prednisone use. This variable has been agreed upon by a panel of experts in the treatment of SLE to be the best single variable quantitative assessment of treatment benefit.

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Only the prednisone dose recorded in the medication record form will be used for these two primary efficacy variables.

Reductions in prednisone use are expected to be without meaningful increase in SLEDAI because of the prednisone dose tapering rules, however this assumption will also be checked by secondary analysis.

Analysis of primary efficacy variable 1 will be by logistic regression analysis of the proportion achieving success controlling for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

Analysis of primary efficacy variable 2 will be by ANOVA with control for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

If there is a study site with fewer than 3 intent-to-treat patients in one treatment group, then this study site's data will be pooled. The step-by-step iterative pooling scheme is described in the following:

- Step 1. Among the group of study sites for which pooling is required (fewer than 3 patients), the study site with the smallest total number of intent-to-treat patients will be selected. This study site and the study site with next smallest total number of intent-to-treat patients among this group will be pooled together and identified as a new study site.
- Step 2. After creation of the new study site described in step 1, all study sites, including the newly created one, with fewer than 3 intent-to-treat patients in one treatment group will be selected. If there are more than two such study sites, then step 1 will be repeated in an iterative manner. If there is no such study site, then no additional pooling will be done.

If there is only one such (fewer than 3 intent-to-treat patients in one treatment group) study site, then this study site and the study site, with the smallest total number of intent-to-treat patients among the remaining study sites, will be pooled together.

The descriptive statistics for the primary efficacy variables by treatment group will be displayed.

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9.3.3 Secondary Efficacy Variables

Secondary efficacy variables include:

- 1) Change from baseline in SLEDAI
- 2) Change from baseline in quality of life assessment by SF-36
- 3) Change from baseline in Krupp Fatigue Score
- 4) Change from baseline in global assessment of disease activity by physician
- 5) Change from baseline in global assessment of disease activity by patient

All secondary efficacy variables will be analyzed by means of a two-way analysis of covariance model with treatment and trial center as factors and baseline (Qualifying Visit) as a covariate. Both treatment-by-baseline and treatment-by-center interactions will be included in the model.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

If there is a study site with fewer than 3 intent-to-treat patients in one treatment group, then this study site's data will be pooled by the pooling scheme described in 9.3.2.

The summary statistics for these efficacy variables by treatment group will be displayed.

9.4 Safety

Changes in laboratory values and incidence of adverse events by treatment group will be displayed by descriptive statistics. The three-treatment-group comparison will be performed by either Cochran-Mantel-Haenszel test or one-way ANOVA.

9.5 Blinded Interim analysis

A limited blinded interim analysis will be performed in order to adjust the sample size to ensure adequate power for primary efficacy variable 2. The limited interim analysis will be carried out under the control of an independent study monitoring board and no information regarding interim treatment efficacy differences will be issued or used in the sample size adjustment.

The limited blinded interim analysis will provide an interim (pooled) estimate of the patient to patient variability within treatment groups for primary efficacy variable 2. This information will be used for adjusting the sample size of the study. The limited interim analysis will be scheduled for the date that the data are complete for the first 60 evaluable patients (the order of evaluable patients will be ranked by the date of randomization). An evaluable patient is defined as one for whom both baseline measurement and at least one post-baseline measurement in prednisone dose have been recorded. Only the prednisone dose data for these 60 patients will be used for interim analysis.

9.6 Sample Size determination

Initial sample size is 190 randomized patients to allow 168 patients completed the study. The sample size will be adjusted to ensure adequate power to detect treatment effects upon primary efficacy variable 2.

Only the prednisone dose data for the first 60 evaluable patients will be used for interim analysis in sample size reestimation. During the interim analysis, all the drug codes will be blinded.

The following statistical methodology of EM algorithm will be conducted for the blinded interim analysis.

Variance Estimate

Since each measurement, percent decrease in prednisone dose, at jth treatment group is assumed to have a normal distribution $N(\mu_j, \sigma^2)$, and its the treatment identification, I_{ij} , $i=1, \dots, n$, $j=1, 2$, or 3, is unknown, EM algorithm, the extension of Gould and Shih (1992) or Shih (1995), will be used in estimating σ^2 . The method is listed in the following:

E-step: Estimate I_{ij} by:

$$\hat{I}_{ij} = \frac{\exp[-(x_i - \mu_j)^2 / 2\sigma^2]}{\exp[-(x_i - \mu_1)^2 / 2\sigma^2] + \exp[-(x_i - \mu_2)^2 / 2\sigma^2] + \exp[-(x_i - \mu_3)^2 / 2\sigma^2]}$$

where $i=1, \dots, n$, $j=1, 2, 3$ and n is the total number of measurements in the interim analysis.

M-step: Estimate μ_j and σ^2 by:

$$\hat{\mu}_j = \frac{\sum_{i=1}^n x_i \hat{I}_{ij}}{\sum_{i=1}^n \hat{I}_{ij}}, \quad j = 1, 2, 3, \quad \hat{\sigma}^2 = \frac{1}{n} \sum_{i=1}^n \sum_{j=1}^3 (x_i - \hat{\mu}_j)^2 \hat{I}_{ij}$$

Iterate E and M steps till convergence and obtain the estimate for σ^2 . The estimates for μ_j , $j=1, 2, 3$, will not be outputed.

Correction Factor in Variance Estimate

If the re-estimated sample size for all three treatment groups is less than 168, then the study will continue as planned; no reduction in sample size will occur. Since the sample size will not be changed¹ when $\lambda = \sigma / \Delta < 5/3$, the seven selected cases with $\lambda \geq 5/3$ are studied. In each case, there are 10 simulations, with three treatments and 20 observations per treatment, to compare hypothetical true σ^2 with the estimated σ^2 by EM algorithm. The means of the estimated values of σ^2 are summarized in the following:

True $\sigma^2=25$ True $\Delta=\mu_3-\mu_1$	$\mu_1 \leq \mu_2 \leq \mu_3$ and $\mu_2 = 1/2 (\mu_1 + \mu_3)$		$\mu_1 < \mu_2 = \mu_3$	
	ANOVA*	EM	ANOVA*	EM
$\lambda = \sigma / \Delta = 5/3$	27.32	16.79	27.11	17.99
$\lambda = \sigma / \Delta = 5/2$	28.4	16.47	28.89	19.73
$\lambda = \sigma / \Delta = 5$	27.88	16.5	26.49	13.15
$\Delta = 0$	25.35	15.35		

- * Unblinded one-way analysis of variance with treatment as factor.

From the above table, the ratios between the means of the estimated values of σ^2 from two different methods are roughly about 2/3. Hence, we suggest that the estimate of σ^2 from EM algorithm should be adjusted by multiplying 1.5, or the corrected estimate of σ^2 is 1.5 times of the estimate of σ^2 from EM algorithm.

Sample Size Reestimation

The sample size will be recalculated based on the corrected re-estimated σ^2 to give 80% power for the two-sided pairwise comparison at the level of 0.025 (due to the Bonferroni's adjustment) assuming the true treatment difference from placebo in primary efficacy variable, percent decrease in prednisone use, is 30%.

- ¹ The sample size estimate of 53 per arm will be yielded to give 80% power for the two-sided pairwise comparison at the level of 0.025 (due to the Bonferroni's adjustment) when $\lambda = \sigma / \Delta = 5/3$.

Sample Size Adjustment Due To Dropout

The sample size for the study will be adjusted according to the observed dropout rate before Dosing Visit 6 from the 60 patients in the interim analysis. The randomized patients who had last measurement in prednisone use before Dosing Visit 6 will be considered as dropouts before Dosing Visit 6. If this adjusted sample size is smaller than 190, then the sample size for the study will not be changed.

Since no relative efficacy results will be available at the interim stage, this interim analysis is an administrative interim analysis. Wittes and Brittain (1990) and Gould and Shih (1992) have shown that the procedure of sample size reestimation inflates the Type I error rate only very minimally (about the order of 10^{-3}), but the gain in maintaining the power can be very substantial. So, no adjustment of Type I error will be made for this study.

9.7 Independent Study Monitoring Board

An independent study monitoring board (ISMB) will be created. The ISMB will perform the following functions:

1. Confidentially monitor key safety parameters for indications that the study should be terminated because of safety considerations.
2. Monitor the generation and confidentiality of the limited interim analysis used to re-estimate sample size.
3. Monitor and provide guidance on any issue related to patient's welfare and the validity of the study, including amendments to the protocol.

The ISMB will include appropriate medical and statistical expertise. ISMB members must be free from conflicts of interest. The ISMB will receive its information from the designated statistician who also performs the confidential limited interim analysis.

References - The following articles have been cited above:

Wittes J, Brittain E. (1990) The role of internal pilot studies in increasing the efficacy of clinical trials. *Statistics in Medicine*, 9, 65-72.

Gould AL, Shih WJ. (1992) Sample size reestimation without unblinding for normally distributed outcomes with unknown variance. *Communication in Statistics (A)*, 21(10), 2833-2853.

Shih WJ. (1995) Sample Size Re-estimation in Clinical Trials. Presented to FDA.

PROTOCOL No. GL94-01

AMENDMENT No. 5

(March 21, 1997)

**A Double-Blind, Randomized Phase II/III Study of GL701 in
Female Patients with Mild to Moderate Systemic Lupus Erythematosus**

PROTOCOL No. GL 94-01

SUMMARY OF AMENDMENTS

1. Amendment No. 1 (Dated - April 25, 1994): Adds measurements of bone mass using dual photon absorptiometry at the Qualifying and Completion visits at one site (Denver Arthritis Clinic).
2. Amendment No. 2 (Dated - July 29, 1994): Changes the requirement for lab specimen collection to the day of the study visits instead of within 10 days prior to study visits. SLEDAI score calculations will be done as the lab results are reported, and subsequent required changes in prednisone dose levels will be telephoned to the patient within a required time frame. All patients who have a 2+ level of urine protein by the urinalysis dipstick at any visit will be required to take a 24 hour urine collection for quantitative urine protein. A long term follow-up visit will be required of those patients who complete GL94-01, but who do not enroll in any of the follow-up studies. Follow-up phone contact will be required for those patients who discontinue study treatment prematurely. Clarifications are made regarding laboratory testing, English language requirements, study medication storage, prednisone use, NSAID use and unblinding procedures.
3. Amendment No. 3 (Dated - November 10, 1994; Only for selected sites): Adds two (2) timepoints for the collection of serum samples for plasma levels of DHEA-S at selected sites. Specimens for DHEA-S will now be drawn at Screening, Dosing Visits 1,2, and 3, and Completion or Termination visits to be assayed and banked by the Genelabs Quality Control Department.
4. Amendment No. 4 (Dated - January 18, 1995): Revises procedures for a change in return of study medication from Simirex to Genelabs. Revises statistical section for the study. Clarifications and changes were made to the following sections: 9.1 Baseline comparability, 9.2 Blinding, 9.3 Efficacy, 9.4 Safety, 9.5 Interim Analysis and 9.6 Sample Size Adjustment.
5. Amendment No. 5 (Dated - March 21, 1997): This amendment revises the analysis plan described in the original protocol GL94-01 and Amendment 4 (dated January 18, 1995, revised July 18, 1995). The analysis plan proposed in this amendment conforms with the analysis plan of the original protocol and clarifies the analysis plan to conform to agreements reached in a telephone conference with the Agency (February 19, 1997). Clarifications and changes were made to the following sections: 9.3 Efficacy, and 9.4 Safety.

PROTOCOL No. GL94-01

AMENDMENT No. 5

(March 21, 1997)

SUMMARY

This amendment revises the analysis plan described in the original protocol GL94-01 and Amendment 4 (dated January 18, 1995, revised July 18, 1995). The analysis plan proposed in this amendment conforms with the analysis plan of the original protocol and clarifies the analysis plan to conform to agreements reached in a telephone conference with the Agency (February 19, 1997).

All analyses will be performed as intent-to-treat analyses. For each efficacy variable, the intent-to-treat analysis will only include patients randomized to treatment who had a baseline measurement, received at least one dose of study drug, and had at least one post-baseline measurement.

Primary Efficacy Variable #1 is clarified to be achievement of a decrease in prednisone dose to 7.5 mg/day or less, and this decrease must be sustained for no less than three consecutive visits, including the scheduled termination visit (i.e., 2 consecutive months), on or after Visit 7.

During the three consecutive study visits:

- a. Any increase in prednisone dose to > 7.5 mg/day at interim visits will violate the definition of responder.
- b. The prednisone dose will be the physician prescribed dose recorded on the Medication Record Form, which will be checked against the dose reported by the patient recorded on the Glucocorticoid Medication Form. If the doses are different, the dose used will be that recorded on the Glucocorticoid Medication Form.
- c. Patients who received stress doses of hydrocortisone for acute (e.g., 1 to 3 day), non-SLE related events (e.g., minor surgery) will be evaluated as nonresponders.

The proportion of responders will be analyzed by logistic regression analysis with treatment as a factor. Baseline variables which attain a 0.05 significance level for association with treatment assignment may be included as covariates.

The Primary Efficacy Variable #1 will also be analyzed in a secondary analysis to allow patients who received stress doses of hydrocortisone for acute non-SLE-related events (e.g., 1 to 3 days for minor surgery) as responders.

In addition, for Primary Efficacy Variable #1, SLEDAI baseline and treatment interaction will be included in the logistic regression model as a secondary analysis.

Primary Efficacy Variable #2 is clarified to be the percent decrease in prednisone dose and will compare the prescribed prednisone (or steroid equivalent) dose at Baseline (Qualifying Visit) and the last visit prednisone (or steroid equivalent) dose using the physician prescribed prednisone dose recorded on the Medication Record Form.

The analysis will be performed by a one-way ANOVA model with treatment as a factor. Baseline variables which attain a 0.05 significance level for association with treatment assignment may be included as covariates.

All secondary efficacy variables will be analyzed by a one-way analysis of covariance model with treatment as a factor and baseline (Qualifying Visit) as a covariate. Treatment-by-baseline interaction will be included in the model.

Changes in laboratory values and incidence of adverse events by treatment group will be displayed by descriptive statistics. For clinically important laboratory values and adverse events by body system, the three-treatment-group comparison will be performed by either Cochran-Mantel-Haenszel test or one-way ANOVA.

PROTOCOL No. GL94-01**AMENDMENT No. 5****(March 21, 1997)****SUMMARY OF CHANGES**

This amendment revises the analysis plan described in the original protocol GL94-01 and Amendment 4 (dated January 18, 1995, revised July 18, 1995). The analysis plan proposed in this amendment conforms with the analysis plan of the original protocol and clarifies the analysis plan to conform to agreements reached in a telephone conference with the Agency (February 19, 1997).

9.3 Efficacy**9.3.1 Patient evaluability for efficacy analysis****Current wording, per Amendment 4, states:**

“All analyses will be performed as intent-to-treat analyses at Dosing Visit 6 except the intent-to-treat analysis for the first primary efficacy variable. For each efficacy variable, the intent-to-treat analysis at Dosing Visit 6 will only include the randomized patients who had baseline measurement and at least one post-baseline measurement on or before Dosing Visit 6. The last measurement on or before Dosing Visit 6 will be analyzed.”

Revised wording:

“All analyses will be performed as intent-to-treat analyses. For each efficacy variable, the intent-to-treat analysis will only include patients randomized to treatment who had a baseline measurement, received at least one dose of study drug, and had at least one post-baseline measurement.”

9.3.2 Primary Efficacy Variables**Present wording states:**

“This study includes two primary efficacy variables. The two variables are

1. Achievement of a sustained decrease in prednisone dose to 7.5 mg/day or less, and this decrease must be sustained for no less than two months, and
2. Percent decrease in prednisone use, comparing final dose with baseline.

The first primary efficacy variable assesses clinically important reduction in daily prednisone use. This variable is specifically designed to reflect treatment's ability to provide benefit consistent with 21 CFR 312 Subpart E status.

The second primary efficacy variable assesses percent reduction achieved in daily prednisone use. This variable has been agreed upon by a panel of experts in the treatment of SLE to be the best single variable quantitative assessment of treatment benefit.

Only the prednisone dose recorded in the medication record form will be used for these two primary efficacy variables.

Reductions in prednisone use are expected to be without meaningful increase in SLEDAI because of the prednisone dose tapering rules, however this assumption will also be checked by secondary analysis.

Analysis of primary efficacy variable 1 will be by logistic regression analysis of the proportion achieving success controlling for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates.

Analysis of primary efficacy variable 2 will be by ANOVA with control for site. Baseline variables which attain a .05 significance level for association with treatment assignment may be included as covariates."

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

If there is a study site with fewer than 3 intent-to-treat patients in one treatment group, then this study site's data will be pooled. The step-by-step iterative pooling scheme is described in the following:

Step 1. Among the group of study sites for which pooling is required (fewer than 3 patients), the study site with the smallest total number of intent-to-treat patients will be selected. This study site and the study site with next smallest total number of intent-to-treat patients among this group will be pooled together and identified as a new study site.

Step 2. After creation of the new study site described in step 1, all study sites, including the newly created one, with fewer than 3 intent-to-treat patients in one treatment group will be selected. If there are more than two such study sites, then step 1 will be repeated in an iterative manner. If there is no such study site, then no additional pooling will be done.

If there is only one such (fewer than 3 intent-to-treat patients in one treatment group) study site, then this study site and the study site, with the smallest total number of intent-to-treat patients among the remaining study sites, will be pooled together.

The descriptive statistics for the primary efficacy variables by treatment group will be displayed.”

Revised wording to state:

“9.3.2 Primary Efficacy Variables

This study includes two primary efficacy variables. The two variables are:

1. Achievement of a decrease in prednisone dose to 7.5 mg/day or less sustained for no less than three consecutive scheduled visits, including the termination visit (i.e., two consecutive months), on or after Visit 7.
2. Percent decrease in prednisone dose and will compare the prescribed prednisone (or steroid equivalent) dose at Baseline (Qualifying Visit) and the last visit prednisone (or steroid equivalent) dose using the physician prescribed prednisone dose recorded on the Medication Record Form.

The first primary efficacy variable assesses a clinically important reduction in daily prednisone dose. This variable is specifically designed to reflect the treatment's ability to provide benefit consistent with 21 CFR 312 Subpart E status.

The second primary efficacy variable assesses percent reduction achieved in daily prednisone dose.

Primary Efficacy Variable #1: By-patient reduction in prednisone dose (Subpart E) to 7.5 mg/day or less, and this decrease must be sustained for no less than three consecutive visits, including the scheduled termination visit (i.e., 2 consecutive months), on or after Visit 7.

During the three consecutive study visits:

- a. Any increase in prednisone dose to > 7.5 mg/day at interim visits will violate the definition of responder
- b. The prednisone dose will be the physician prescribed dose recorded on the Medication Record Form, which will be checked against the dose reported by the patient recorded on the Glucocorticoid Medication Form. If the doses are different, the dose used will be that recorded on the Glucocorticoid Medication Form
- c. Patients who received stress doses of hydrocortisone for acute (e.g., 1 to 3 day), non-SLE related events (e.g., minor surgery) will be evaluated as non-responders.

The proportion of responders will be analyzed by logistic regression analysis with treatment as a factor. Baseline variables which attain a 0.05 significance level for association with treatment assignment may be included as covariates.

The Primary Efficacy Variable #1 will also be analyzed in a secondary analysis to allow patients who received stress doses of hydrocortisone for acute non-SLE-related events (e.g., 1 to 3 days for minor surgery) as responders.

In addition, for Primary Efficacy Variable #1, SLEDAI baseline and treatment interaction will be included in the logistic regression model as a secondary analysis.

Primary Efficacy Variable #2: The percent decrease in prednisone dose will compare the prescribed prednisone (or steroid equivalent) dose at Baseline (Qualifying Visit) and the last visit prednisone (or steroid equivalent) dose using the physician prescribed prednisone dose recorded on the Medication Record Form.

The analysis will be performed by a one-way ANOVA model with treatment as a factor. Baseline variables which attain a 0.05 significance level for association with treatment assignment may be included as covariates.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

In addition, for Primary Efficacy Variable #2, SLEDAI baseline and treatment interaction will be included in the ANOVA model.

The descriptive statistics for the primary efficacy variables by treatment group will be displayed. **Also, the descriptive statistics for the primary efficacy variables by treatment group and center will be displayed to examine whether treatment effects are consistent among the centers."**

9.3.3 Secondary Efficacy Variables

Presently reads:

"Secondary efficacy variables include:

- 1) Change from baseline in SLEDAI
- 2) Change from baseline in quality of life assessment by SF-36
- 3) Change from baseline in Krupp Fatigue Score
- 4) Change from baseline in global assessment of disease activity by physician
- 5) Change from baseline in global assessment of disease activity by patient

All secondary efficacy variables will be analyzed by means of a two-way analysis of covariance model with treatment and trial center as factors and baseline (Qualifying Visit) as a covariate. Both treatment-by-baseline and treatment-by-center interactions will be included in the model.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

If there is a study site with fewer than 3 intent-to-treat patients in one treatment group, then this study site's data will be pooled by the pooling scheme described in 9.3.2.

The summary statistics for these efficacy variables by treatment group will be displayed."

Revised to read:

"9.3.3 Secondary Efficacy Variables

Secondary efficacy variables include:

- 1) Change from baseline in SLEDAI
- 2) Change from baseline in quality of life assessment by SF-36
- 3) Change from baseline in Krupp Fatigue Score
- 4) Change from baseline in global assessment of disease activity by physician
- 5) Change from baseline in global assessment of disease activity by patient

All secondary efficacy variables will be analyzed by means of a one-way analysis of covariance model with treatment as a factor and baseline (Qualifying Visit) as a covariate. Treatment-by-baseline interaction will be included in the model.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

The summary statistics for the secondary efficacy variables by treatment group will be displayed. Also, the summary statistics for the secondary efficacy variables by treatment group and center will be displayed to examine whether treatment effects are consistent among the centers."

9.4 Safety

Presently reads:

"Changes in laboratory values and incidence of adverse events by treatment group will be displayed by descriptive statistics. The three-treatment-group comparison will be performed by either Cochran-Mantel-Haenszel test or one-way ANOVA."

Revised to read:

"Changes in laboratory values and incidence of adverse events by treatment group will be displayed by descriptive statistics. **For clinically important laboratory values and adverse events by body system**, the three-treatment-group comparison will be performed by either Cochran-Mantel-Haenszel test or one-way ANOVA."

PROTOCOL No. GL94-01**AMENDMENT No. 5**

(March 21, 1997)

This amendment revises the analysis plan described in the original protocol GL94-01 and last modified by Amendment 4 (dated January 18, 1995, revised July 18, 1995)

9. STUDY ANALYSIS**9.F Baseline Comparability**

Baseline values, including demographic variables and efficacy variables, will be compared among the treatment groups by Cochran-Mantel-Haenszel test or one-way ANOVA with treatment as factor. Variables attaining statistical significance at the level of 0.05 will be included in the primary efficacy analyses to examine the effect of the imbalance of such variables among the treatment groups.

The baseline value for all variables will be the last value measured or obtained prior to initiation of study treatment. Age is age on the day of first study treatment.

9.2 Blinding

Patients, investigators, all persons involved in running the study, and all employees of the sponsor except for a designated statistician are blinded to patient treatment assignments. No unblinding will take place until after all patients in the study have completed the blinded portion of the study and all data from the blinded portion of the study have completed all data verification and all data query resolution.

All decisions regarding admissibility of data for any patient for analysis and sub-group analysis will be made prior to the unblinding to anyone of the treatment assignment for that patient. Since data questions may surface during analysis, this requires maintenance of the blind until all data verification and all data query resolution are completed. Reasons for all data exclusions will be documented. Any data exclusion which has to be made after unblinding will be noted and explained and its impact on the results will be evaluated.

9.3 Efficacy

All statistical tests performed will be two-sided, and a level of 0.05 will be used to declare statistical significance.

9.3.1 Patient Evaluability for Efficacy Analysis

All analyses will be performed as intent-to-treat analyses. For each efficacy variable, the intent-to-treat analysis will only include patients randomized to treatment who had a baseline measurement, received at least one dose of study drug, and had at least one post-baseline measurement.

9.3.2 Primary Efficacy Variables

This study includes two primary efficacy variables. The two variables are:

1. Achievement of a decrease in prednisone dose to 7.5 mg/day or less sustained for no less than three consecutive scheduled visits, including the termination visit (i.e., two consecutive months), on or after Visit 7
2. Percent decrease in prednisone dose will compare the prescribed prednisone (or steroid equivalent) dose at Baseline (Qualifying Visit) and the last visit prednisone (or steroid equivalent) dose using the physician prescribed prednisone dose recorded on the Medication Record Form

The first primary efficacy variable assesses a clinically important reduction in daily prednisone dose. This variable is specifically designed to reflect the treatment's ability to provide benefit consistent with 21 CFR 312 Subpart E status.

The second primary efficacy variable assesses percent reduction achieved in daily prednisone dose.

Primary Efficacy Variable #1: By-patient reduction in prednisone dose (Subpart E) to 7.5 mg/day or less, and this decrease must be sustained for no less than three consecutive visits, including the scheduled termination visit (i.e., 2 consecutive months), on or after Visit 7.

During the three consecutive study visits:

1. Any increase in prednisone dose to > 7.5 mg/day at interim visits will violate the definition of responder.

2. The prednisone dose will be the physician prescribed dose recorded on the Medication Record Form, which will be checked against the dose reported by the patient recorded on the Glucocorticoid Medication Form. If the doses are different, the dose used will be that recorded on the Glucocorticoid Medication Form.
3. Patients who received stress doses of hydrocortisone for acute (e.g., 1 to 3 day), non-SLE related events (e.g., minor surgery) will be evaluated as non-responders.

The proportion of responders will be analyzed by logistic regression analysis with treatment as a factor. Baseline variables which attain a 0.05 significance level for association with treatment assignment may be included as covariates.

The Primary Efficacy Variable #1 will also be analyzed in a secondary analysis to allow patients who received stress doses of hydrocortisone for acute non-SLE-related events (e.g., 1 to 3 days for minor surgery) as responders.

In addition, for Primary Efficacy Variable #1, SLEDAI baseline and treatment interaction will be included in the logistic regression model as a secondary analysis.

Primary Efficacy Variable #2: The percent decrease in prednisone dose will compare the prescribed prednisone (or steroid equivalent) dose at Baseline (Qualifying Visit) and the last visit prednisone (or steroid equivalent) dose using the physician prescribed prednisone dose recorded on the Medication Record Form.

The analysis will be performed by a one-way ANOVA model with treatment as a factor. Baseline variables which attain a 0.05 significance level for association with treatment assignment may be included as covariates.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

In addition, for Primary Efficacy Variable #2, SLEDAI baseline and treatment interaction will be included in the ANOVA model.

The descriptive statistics for the primary efficacy variables by treatment group will be displayed.

Also, the descriptive statistics for the primary efficacy variables by treatment group and center will be displayed to examine whether treatment effects are consistent among the centers.

9.3.3 Secondary Efficacy Variables

Secondary efficacy variables include:

- 1) Change from baseline in SLEDAI
- 2) Change from baseline in quality of life assessment by SF-36
- 3) Change from baseline in Krupp Fatigue Score
- 4) Change from baseline in global assessment of disease activity by physician
- 5) Change from baseline in global assessment of disease activity by patient

All secondary efficacy variables will be analyzed by means of a one-way analysis of covariance model with treatment as a factor and baseline (Qualifying Visit) as a covariate. Treatment-by-baseline interaction will be included in the model.

Bonferroni's method for adjustment for multiple comparisons will be used for the following comparisons:

- i) DHEA 100 mg/day vs. placebo.
- ii) DHEA 200 mg/day vs. placebo

The summary statistics for the secondary efficacy variables by treatment group will be displayed. Also, the summary statistics for the secondary efficacy variables by treatment group and center will be displayed to examine whether treatment effects are consistent among the centers.

9.4 Safety

Changes in laboratory values and incidence of adverse events by treatment group will be displayed by descriptive statistics. For clinically important laboratory values and adverse events by body system, the three-treatment-group comparison will be performed by either Cochran-Mantel-Haenszel test or one-way ANOVA.

9.5 Blinded Interim Analysis

A limited blinded interim analysis will be performed in order to adjust the sample size to ensure adequate power for primary efficacy variable 2. The limited interim analysis will be carried out

under the control of an independent study monitoring board and no information regarding interim treatment efficacy differences will be issued or used in the sample size adjustment.

The limited blinded interim analysis will provide an interim (pooled) estimate of the patient to patient variability within treatment groups for primary efficacy variable 2. This information will be used for adjusting the sample size of the study. The limited interim analysis will be scheduled for the date that the data are complete for the first 60 evaluable patients (the order of evaluable patients will be ranked by the date of randomization). An evaluable patient is defined as one for whom both baseline measurement and at least one post-baseline measurement in prednisone dose have been recorded. Only the prednisone dose data for these 60 patients will be used for interim analysis.

9.6 Sample Size Determination

Initial sample size is 190 randomized patients to allow 168 patients completed the study. The sample size will be adjusted to ensure adequate power to detect treatment effects upon primary efficacy variable 2.

Only the prednisone dose data for the first 60 evaluable patients will be used for interim analysis in sample size re-estimation. During the interim analysis, all the drug codes will be blinded.

The following statistical methodology of EM algorithm will be conducted for the blinded interim analysis.

Variance Estimate

Since each measurement, percent decrease in prednisone dose, at j th treatment group is assumed to have a normal distribution $N(\mu_j, \sigma^2)$, and its the treatment identification, I_{ij} , $i=1, \dots, n$, $j=1, 2$, or 3 , is unknown, EM algorithm, the extension of Gould and Shih (1992) or Shih (1995), will be used in estimating σ^2 . The method is listed in the following:

E-step: Estimate I_{ij} by:

where $i=1, \dots, n$, $j=1, 2, 3$ and n is the total number of measurements in the interim analysis.

M-step: Estimate μ_j and σ^2 by:

$$\mu_j = \frac{\sum_{i=1}^n x_i I_{ij}}{\sum_{i=1}^n I_{ij}}, j = 1, 2, 3, \sigma^2 = \frac{1}{n} \sum_{i=1}^n \sum_{j=1}^3 (x_{su} - \mu_j)^2$$

Iterate E and M steps till convergence and obtain the estimate for σ^2 . The estimates for $\mu_j, j=1, 2, 3$, will not be outputted.

Correction Factor in Variance Estimate

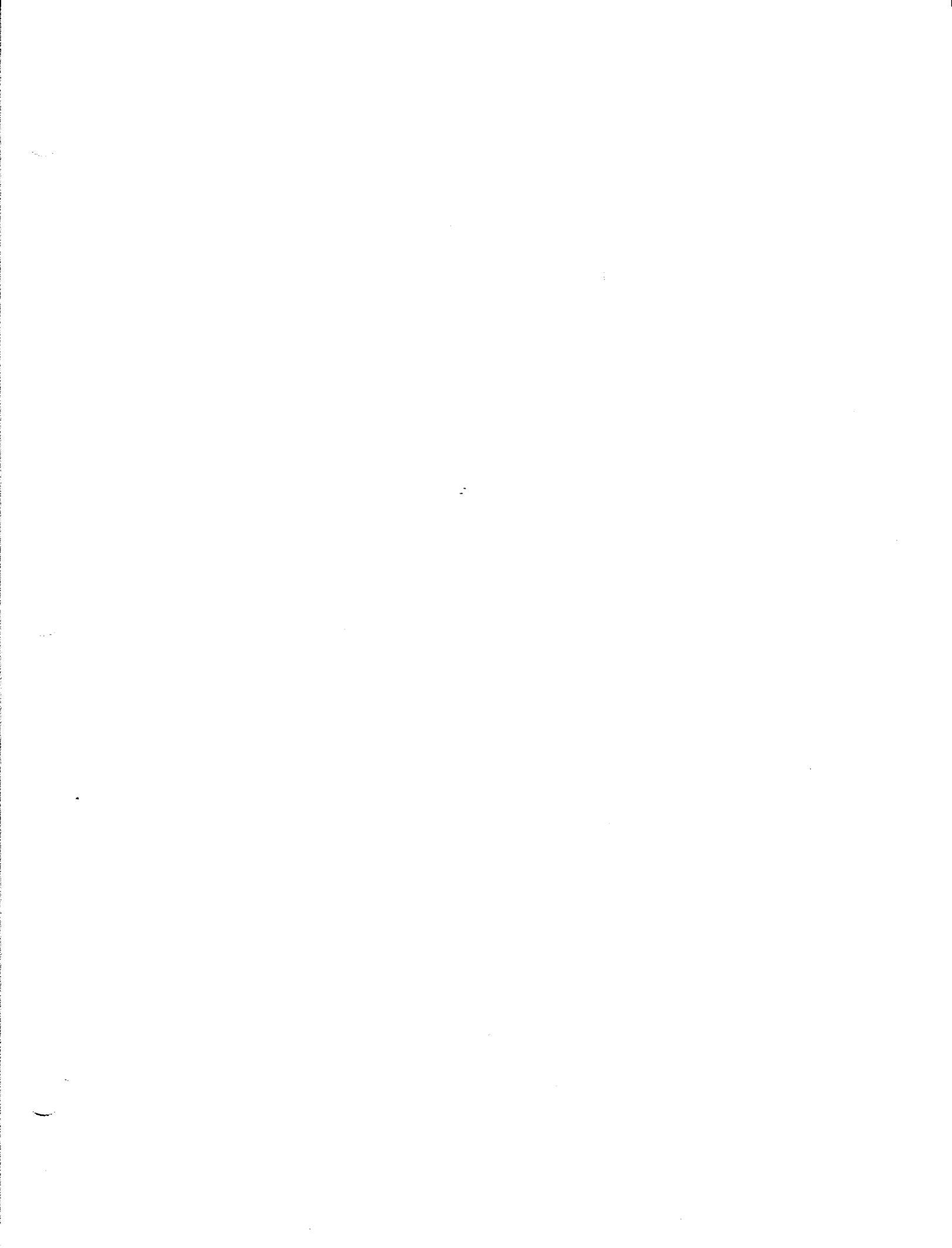
If the re-estimated sample size for all three treatment groups is less than 168, then the study will continue as planned; no reduction in sample size will occur. Since the sample size will not be changed¹ when $\lambda = \sigma / \Delta < 5/3$, the seven selected cases with $\lambda \geq 5/3$ are studied. In each case, there are 10 simulations, with three treatments and 20 observations per treatment, to compare hypothetical true σ^2 with the estimated σ^2 by EM algorithm. The means of the estimated values of σ^2 are summarized in the following:

True $\sigma^2=25$ True $\Delta=\mu_3-\mu_1$	$\mu_1 \leq \mu_2 \leq \mu_3$ and $\mu_2 = (\mu_1 + \mu_3)/2$		$\mu_1 < \mu_2 = \mu_3$	
	ANOVA*	EM	ANOVA*	EMEM
$\lambda = \sigma/\Delta = 5/3$	27.32	16.79	27.11	17.99
$\lambda = \sigma/\Delta = 5/2$	28.4	16.47	28.89	19.73
$\lambda = \sigma/\Delta = 5$	27.88	16.5	26.49	13.15
$\Delta = 0$	25.35	15.35		

* Unblinded one-way analysis of variance with treatment as factor.

From the above table, the ratios between the means of the estimated values of σ^2 from two different methods are roughly about 2/3. Hence, we suggest that the estimate of σ^2 from EM algorithm should be adjusted by multiplying 1.5, or the corrected estimate of σ^2 is 1.5 times of the estimate of σ^2 from EM algorithm.

¹ The sample size estimate of 53 per arm will be yielded to give 80% power for the two-sided pairwise comparison at the level of 0.025 (due to the Bonferroni's adjustment) when $\lambda = \sigma/\Delta = 5/3$.



Sample Size Re-estimation

The sample size will be recalculated based on the corrected re-estimated σ^2 to give 80% power for the two-sided pairwise comparison at the level of 0.025 (due to the Bonferroni's adjustment) assuming the true treatment difference from placebo in primary efficacy variable, percent decrease in prednisone use, is 30%.

Sample Size Adjustment Due To Dropout

The sample size for the study will be adjusted according to the observed dropout rate before Dosing Visit 6 from the 60 patients in the interim analysis. The randomized patients who had last measurement in prednisone use before Dosing Visit 6 will be considered as dropouts before Dosing Visit 6. If this adjusted sample size is smaller than 190, then the sample size for the study will not be changed.

Since no relative efficacy results will be available at the interim stage, this interim analysis is an administrative interim analysis. Wittes and Brittain (1990) and Gould and Shih (1992) have shown that the procedure of sample size reestimation inflates the Type I error rate only very minimally (about the order of 10^{-3}), but the gain in maintaining the power can be very substantial. So, no adjustment of Type I error will be made for this study.

9.7 Independent Study Monitoring Board

An independent study monitoring board (ISMB) will be created. The ISMB will perform the following functions:

1. Confidentially monitor key safety parameters for indications that the study should be terminated because of safety considerations.
2. Monitor the generation and confidentiality of the limited interim analysis used to re-estimate sample size.
3. Monitor and provide guidance on any issue related to patient's welfare and the validity of the study, including amendments to the protocol.

The ISMB will include appropriate medical and statistical expertise. ISMB members must be free from conflicts of interest. The ISMB will receive its information from the designated statistician who also performs the confidential limited interim analysis.

The ISMB will include appropriate medical and statistical expertise. ISMB members must be free from conflicts of interest. The ISMB will receive its information from the designated statistician who also performs the confidential limited interim analysis.

References:

Wittes J, Brittain E. (1990) The role of internal pilot studies in increasing the efficacy of clinical trials. *Statistics in Medicine*, 9, 65-72.

Gould AL, Shih WJ. (1992) Sample size reestimation without unblinding for normally distributed outcomes with unknown variance. *Communication in Statistics (A)*, 21(10), 2833-2853.