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CLINICAL TRIAL PROTOCOL

Phase III Study

A Multicenter, Randomized, Double-Blind, Placebo Controlled Study Of  
GL701 In Female Patients With Active Systemic Lupus Erythematosus

Protocol No.: GL95-02

Genelabs Technologies, Inc.  
505 Penobscot Drive  
Redwood City, CA 94063-4738  
650-369-9500

Date: January 31, 1996

I have received and read the Investigational Drug Brochure for GL701 dated 12/93, the protocol dated January 31, 1996, the Amendments 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  
Institution

\_\_\_\_\_  
Date

\_\_\_\_\_  
Kenneth E. Schwartz, M.D.  
Sr. Medical Director  
Genelabs Technologies, Inc.

\_\_\_\_\_  
Date

## PROPRIETARY STATEMENT

This protocol contains information that is proprietary to Genelabs Technologies, Inc. and is provided for the purpose of conducting a clinical trial. The contents of this protocol may be disclosed to study personnel and an Institutional Review Board as appropriate and necessary. The contents of the protocol may not be disclosed to any other parties without prior written permission from Genelabs Technologies, Inc. These restrictions apply to any subsequent modifications that may be made to the protocol.

PROTOCOL GL95-02

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF  
GL701 IN FEMALE PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

INVESTIGATOR: Multiple

MONITOR: Kenneth E. Schwartz, M.D.  
Genelabs Technologies, Inc.  
Telephone: (650) 562-1510  
Pager#: (800) 396-1559

MANAGER: Betty J. Quarles, B.S.  
Genelabs Technologies, Inc.  
Telephone: (650) 562-1425

CLINICAL RESEARCH ASSOCIATE: Karen Colbert  
Genelabs Technologies, Inc.  
Telephone: (650) 562-1465

Bettina Sporkenbach, RN  
Genelabs Technologies, Inc.  
Telephone: (650) 562-1423

Natalie Lomax  
Regional CRA  
Telephone: (301) 725-0680

BIostatistician: Huang Hsu, Ph.D.  
ACRO  
Telephone: (201) 993-8488

CENTRAL LABORATORY: Covance

Genelabs Technologies, Inc.  
505 Penobscot Drive  
Redwood City, CA 94063-4738  
Fax: (650) 368-3198

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TABLE OF CONTENTS

1.	<u>BACKGROUND AND RATIONALE</u>	6	
1.1	Systemic Lupus Erythematosus	6	
1.2	DHEA	8	
1.3	Role of DHEA In SLE	10	
1.4	Clinical Studies of DHEA	10	
1.5	Clinical Studies of DHEA in SLE	12	
1.6	Estrogen Administration and Endometrial Hyperplasia	15	
2.	<u>STUDY OBJECTIVES</u>	18	
3.	<u>STUDY SYNOPSIS</u>	18	
4.	<u>PATIENT ELIGIBILITY</u>	19	
4.1	Inclusion Criteria	19	
4.2	Exclusion Criteria	20	
4.3	Qualification for Study	21	
4.4	Assignment of Treatment	21	
4.5	Treatment Period	21	
4.6	Concomitant Medications	22	
5.	<u>STUDY DRUG FORMULATION AND PACKAGING</u>	23	
5.1	GL701	23	
6.	<u>STUDY ACTIVITIES</u>	24	
6.1	Screening Visit	25	
6.2	Qualifying Visit	26	
6.3	Quarterly Dosing Visits	28	
6.4	Completion Visit or Termination Visit	29	
6.5	Follow-up for All Patients	31	
6.6	Conditions for Early Termination	31	
6.7	Post-Completion Visit	32	
7.	<u>CLINICAL EFFICACY EVALUATIONS</u>	33	
8.	<u>LABORATORY EVALUATIONS AND DEXA SCANS</u>	33	
8.1	24 Hour Urine	34	
8.2	Local Lab	34	
8.3	Genelabs	35	
8.4	PA Dual Energy X-ray Absorptiometry (DEXA) Scans	35	
9.	<u>ADVERSE EVENTS</u>	35	
9.1	Adverse Event Reporting	35	
9.2	Serious Adverse Events	36	
9.3	Serious, Unexpected, Drug-Related Adverse Events	37	
10.	<u>STUDY ADMINISTRATION</u>	37	
10.1	Institutional Review Board	37	
10.2	Informed Consent	38	
10.3	Source Documentation	39	

10.4	Drug Accountability	39	
10.5	Record Retention	40	
10.6	Case Report Forms	41	
10.7	Monitoring the Study	41	
10.8	Study Amendment	42	
10.9	Final Study Report	42	
11.	<u>TEST OF SUCCESS: CRITERIA</u>	42	
11.1	Primary Efficacy Variable	42	
11.2	Secondary Efficacy Variable	43	
11.3	Clinical Deterioration	44	
12.	<u>STATISTICAL CONSIDERATIONS</u>	45	
12.1	Sample Size Determination	45	
12.2	Population	46	
12.3	Investigational Center Pooling Algorithm	46	46
12.4	Primary Efficacy Analysis	46	
12.5	Secondary Efficacy Analysis	46	
12.6	Safety Variables	47	
13.	<u>PUBLICATION</u>	47	
13.1	Publication by Genelabs		47
13.2	Publication by Institution or Principal Investigator		47
14.	<u>REFERENCES</u>	48	
15.	<u>APPENDICES</u>	54	
15.1	ACR Criteria for Diagnosis of Systemic Lupus Erythematosus	55	
15.2	SLEDAI Score for Disease Progression	57	
15.3	SYSTEMIC LUPUS ACTIVITY MEASURE (SLAM)	58	
15.4	Equivalent Dosages of Glucocorticoid	61	
15.5	Procedures for Processing and Shipping GL701	62	
15.6	GENERAL CLINICAL SAFETY LABORATORY EVALUATIONS	65	
15.7	Procedures for DEXA Scanning	68	
15.8	Schedule of Events	69	
15.9	Transvaginal Ultrasound and Endometrial Biopsies	71	

## 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 occurring 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, 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. 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).

Age, genetic factors and 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). Epidemiologic studies have failed to confirm the association between low DHEA levels and osteoporosis (Nordin et al, 1985; Barrett-Conner et al, 1993). 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).

The placenta is the major source of the large quantity of estrogens produced during pregnancy. In the human, there is little or no steroid 17 $\alpha$ -hydroxylase activity in the placenta, and consequently, there is little if any conversion of C-21 steroids to C-19 steroids; thus the placenta does not further metabolize progesterone. The placenta has a remarkable capacity for aromatization of C-19 steroids, however, and it efficiently

converts androstenedione, testosterone and DHEA to estrone and estradiol (Casey, 1992).

The fetal adrenal gland secretes approximately 100 to 200 mg steroid per day, the principal secretory products being DHEA-S and pregnenolone sulfate. DHEA-S undergoes hydroxylation to 16 $\alpha$ -hydroxy DHEA-S in the fetal liver. Approximately 90% of the estriol excreted in near-term urine is derived from the placental aromatization of 16 $\alpha$ -hydroxy DHEA-S of fetal origin. In addition to its role in providing the precursors for placental estrogen formation, its secretions may participate in the biochemical events leading to initiation of parturition and fetal lung maturation (Casey, 1992).

### 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 litter mates.

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 upregulating 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. Three (3) studies of the safety and therapeutic potential of DHEA in patients with mild to moderate lupus have been initiated to date. Phase I Study (ongoing): In an open label Phase I study, 10 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, 1994). Six patients continued treatment with DHEA for a total of 6 months.

Overall, DHEA was well tolerated. Adverse events included acneiform dermatitis in four patients. One patient discontinued due to this adverse event, while other patients responded to topical therapy. Hirsutism was observed in 2 patients.

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 antiinflammatory drugs, hydroxychloroquine, or low dose glucocorticoids (prednisone,  $\leq$  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 range<sup>1</sup> 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.

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 (Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)

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

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  $9.8 \pm 1.7$  vs.  $6.1 \pm 1.3$  for those patients on placebo ( $p = 0.10$ ). The prednisone equivalent dose was  $15.8 \pm 3.0$  mg/day for DHEA and  $7.7 \pm 1.2$  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. <sup>2</sup>	adj. <sup>3</sup>
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	0.022
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

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%).

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.

A double blind, randomized, placebo-controlled trial of DHEA (hereafter referred to as GL701) in patients with steroid-dependent SLE is ongoing in 18 centers across the US. As of January 1996, 192 patients have been randomized to receive placebo or GL701 in doses of 100 or 200 mg. No patient has dropped out because of drug-related toxicity and there have been no serious adverse events that were interpreted by the investigator to be related to the use of the drug.

The purpose of the present study is to evaluate the safety and efficacy of GL701 to improve disease manifestations in patients with active SLE. To avoid the confounding effects of changes in concomitant medications, this study is designed to minimize changes in doses of prednisone, methotrexate, azathioprine and hydroxychloroquine. To be eligible for this study patients must have active SLE and be receiving stable doses of medications for its treatment. There must also be a minimum level of disease activity present to permit assessment of drug effect on disease activity. For this study, activity will be assessed via the Systemic Lupus Activity Measure (SLAM).

## 1.6 Estrogen Administration and Endometrial Hyperplasia

<sup>2</sup> t test, 2-sided

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

Serum estradiol increased to pre-menopausal levels in some postmenopausal SLE patients receiving GL701 during clinical trials. Since the potential for endometrial hyperplasia during chronic DHEA administration is unknown, all post-menopausal patients with an intact uterus, regardless of hormonal replacement status, who are participating in Study GL95-02, or are up to six months post-completion, will be requested to undergo transvaginal ultrasound of the uterus. Those with abnormal endometrial findings will be eligible to undergo endometrial biopsy through this amendment.

Patients with endometrial hyperplasia will be requested to receive treatment with medroxyprogesterone acetate, 10 mg/day for 3 months, and will undergo a repeat endometrial biopsy to assess reversibility of the lesion.

DHEA undergoes conversion into more potent androgens and/or estrogens in peripheral target tissues through the action of various steroidogenic and metabolizing enzymes in each of these tissues (Labrie, 1995). In some tissues, the conversion remains primarily androgenic; in others, it is estrogenic (Labrie, 1995, 1997).

These steroid pathways are diagrammatically illustrated below:

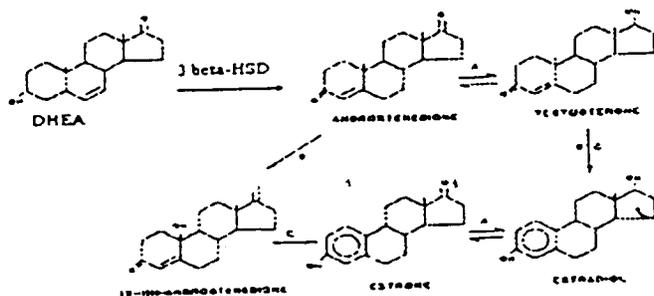


Figure: Aromatization and androgenic conversion of DHEA. Enzymes: (A) 17 beta-HSD; (B) 17 beta-HSD; (C) aromatase

modified from Parker LN. Adrenal androgen metabolism. In Adrenal Androgens in Clinical Medicine. Academic Press, 1989, p8.

Effects of Chronic Dosing with GL701 on Serum Estradiol Levels in Postmenopausal SLE Patients

Genelabs Study GL94-01 enrolled 191 women with mild to moderate systemic lupus erythematosus (SLE). In premenopausal women, mean concentrations of serum estradiol in premenopausal patients with SLE who were not receiving exogenous estrogens or progestins at baseline were 95.2, 106.9, and 105.6 pg/ml in the placebo, GL701 100 mg and GL701 200 mg treatment groups, respectively. At last visit, mean estradiol concentrations were 97.0, 101.0, and 115.1 pg/ml in the placebo, GL701 100 mg and GL701 200 mg treatment groups, respectively.

The mean, total serum estradiol levels observed in premenopausal women are difficult to interpret, as samples were not timed to menses. Relative to placebo, however, the mean estradiol levels in the GL701 200-mg group was within normal range for normal premenopausal women. (Laboratory reference ranges for estradiol are up to 205 pg/ml follicular phase; up to 400 pg/ml midcycle, and up to 270 pg/ml during the luteal phase.) In premenopausal SLE patients with amenorrhea, however, reduces sex hormone binding globulin and increased total estradiol levels would require surveillance of endometrial histology.

In the post-menopausal SLE patients who received GL-701, dose related increases in serum estradiol and testosterone were observed (see Table below). In some cases, these levels approached premenopausal levels.

Estradiol in Post-Menopausal SLE Patients (Patients Who Received Exogenous Estrogens or Progestins are Excluded)		
Treatment Group	Mean ( $\pm$ SD) at Baseline (pg/ml)	Mean Change ( $\pm$ SD) from Baseline to Last Visit (pg/ml)
Placebo	17.6 (30.3) (n=12)	-12.2 (30.4) (n=12) Range (-99.3/13.7)
GL701 100 mg/day	2.7 (3.5) (n=13)	49.4§ (76.7) (n=13) Range (0.0/254.7)
GL701 200 mg/day	25.6 (48.3) (n=4)	129.3§§ (163.8) (n=4) Range (46.0/375.0)

§P=0.0061, GL701 100mg vs. placebo, change from baseline to last visit, one way ANOVA  
§§P=0.005, GL701 200mg vs. placebo, change from baseline to last visit, one way ANOVA

As these elevations in serum estradiol may be sustained and unopposed (i.e., no concomitant progestin treatment), appropriate gynecologic surveillance is warranted.

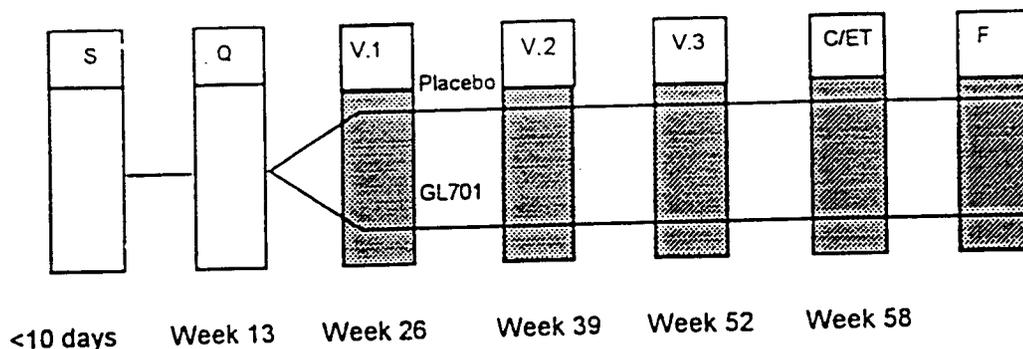
The association of unopposed estrogen administration to endometrial hyperplasia and cancer was reported in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial; a three-year randomized trial of placebo, unopposed estrogen (0.625mg. conjugated equine estrogen (CEE)), or three estrogen-progestin (CEE and medroxy progesterone acetate 10mg/day) regimens in 875 postmenopausal women. (The Writing Group for the PEPI Trial, 1995; 1996) Risk of adenomatous or atypical endometrial hyperplasia was about 1% among women assigned to the placebo group or to any of the estrogen-progestin combinations, whereas it was 34% among women assigned to treatment with estrogen alone.

For women receiving conjugated estrogens alone, the prevalence of some type of hyperplasia as their most abnormal result during the first, second, and third years of observation were 21%, 29.4%, and 16.8%, respectively. Of these women, 12.5%, 11.8%, and 10.1% had complex (adenomatous) or atypical hyperplasia during these same time periods. Only one woman, who in fact received placebo and no exogenous or progestogenic steroids, developed adenocarcinoma of the endometrium during the three-year observation period. Medical intervention, when attempted, converted the endometrium to normal in all participants with simple (cystic) and complex (adenomatous) hyperplasia. In women with atypical hyperplasia, medical intervention was effective in eight of 10 women in whom it was tried (PEPI Writing Group, 1996).

The relevance of the PEPI study findings as to postmenopausal women receiving DHEA chronically is unknown, particularly as there has been no assessment of endometrial changes in postmenopausal women receiving chronic oral DHEA administration, and it is unknown whether conversion of DHEA to androgenic pathways would be protective against endometrial hyperplasia.

## 2. STUDY OBJECTIVES

- 2.1 The primary objective of this study will be to demonstrate improvement in the disease and or its symptoms.
- 2.2 Safety and tolerability of 200 mg/day GL701 vs. placebo will be assessed by collection of adverse event data, and laboratory test results. The study plan is shown below.



S= Screen, Q= Qualifying, C/ET= Completion/Early Termination, V= Visit, F= Follow-up

### 3. STUDY SYNOPSIS

This Multicenter double-blind, randomized, placebo-controlled study will enroll up to approximately 350 patients. Fifty additional patients will be added, however, enrollment will close at the end of the first quarter-1998 (March 31, 1998) if the full complement of approximately 50 additional patients cannot be recruited during that period. This study is composed of three periods: A Screening/Qualifying period, a double-blind placebo-controlled treatment period and an adverse event follow-up assessment period. During the Screening/Qualifying period patients will have a 7 to 10 day "run-in" period with SLAM and SLEDAI measurements at Screening and Qualifying Visits. Both SLAM determinations must be  $\geq 7$  (excluding points assessed for ESR) and for patients enrolled subsequent to Amendment 1 both SLEDAI determinations must be  $> 2$ . The mean of both measurements will be used as the baseline value. Mean baseline SLEDAI and patient VAS scores will also be calculated based upon Screening and Qualifying Visits. During the double-blind treatment period patients will be randomly assigned to receive GL701 200 mg/day or placebo. Patients will remain on the same blinded treatment for the duration of the study. Patient accrual is expected to last approximately 12 months. Following the Screening/Qualifying period, patients will return to the clinic at Weeks 13, 26, 39, and 52 (Completion/Early Termination) followed by a 6-week post-study completion adverse event follow-up assessment by telephone. All adverse events will be followed until resolution or stabilization.

Scheduled visit evaluations will include physical examinations, laboratory determinations, Systemic Lupus Activity Measure (SLAM) determination, SLE Disease Activity Index (SLEDAI) determination, physician global assessment by 10 cm Visual Analog Scale (VAS), patient overall assessments by 10 cm VAS, SF-36 and Krupp Fatigue Severity Scale (KFSS), ACR Criteria at baseline and the SLICC (Systemic Lupus International Cooperating Clinics) Damage Index at baseline and study Completion/Early Termination. To assess bone density of the lumbar spine and proximal femur, dual energy x-ray absorptiometry (DEXA) scans will be performed at some investigator sites on patients who have received steroids for at least 6 months prior to study entry.

Patients who complete the full 12 months of treatment with study drug will be eligible to receive GL701 in an open label safety study.

#### 4. PATIENT ELIGIBILITY

##### 4.1 Inclusion Criteria

- 4.1.1 Female patients, at least 18 years of age.
- 4.1.2 Patients diagnosed with SLE  $\geq$  6 months according to the 1982 American College of Rheumatology Criteria.
- 4.1.3 A SLAM score of  $\geq$  7 at both the screening and qualifying visits, excluding points assessed for ESR.
- 4.1.4 Patients treated for SLE with doses of prednisone  $\leq$  10 mg/day (including those on NO glucocorticoid therapy) unchanged for  $\geq$  6 weeks prior to study entry (see Section 4.6.4 for patients receiving alternate day prednisone dosing).
- 4.1.5 Patients treated with azathioprine, methotrexate, and/or Plaquenil must be on a stable dose with no change in dose for at least 6 weeks preceding the study.
- 4.1.6 Women of child-bearing potential must have a negative pregnancy test (at the Qualifying Visit, prior to study entry) and use a reliable form of birth control while participating in the study (excluding estrogen containing oral contraceptives) which may include: documented tubal ligation or vasectomy, IUD, condom with spermicide, or diaphragm with spermicide. Patients on estrogen containing oral contraceptives must undergo a 3 week washout period prior to the study Screening Visit. Non-contraceptive, estrogen replacement therapy is permitted.
- 4.1.7 Patient is willing and able to sign an Informed Consent Form.
- 4.1.8 A SLEDAI score of  $>2$  at both the Screening and Qualifying Visits for patients enrolled under this amendment.

##### 4.2 Exclusion Criteria

- 4.2.1 History of breast cancer or malignancy of the reproductive tract organs (except cervical carcinoma, surgically cured with no evidence of disease for 5 years).
- 4.2.2 Patients receiving hemodialysis treatment.
- 4.2.3 Patients receiving treatment with ACTH within the 3 months preceding study entry.
- 4.2.4 Patients receiving androgens, immunoglobulins, cyclophosphamide, cyclosporin A, or other immunosuppressive agents, except azathioprine or methotrexate, within the last 3 months.
- 4.2.5 Patients with known hypersensitivity to DHEA or the inactive ingredients used in the GL701 formulation (cornstarch, lactose, magnesium stearate).
- 4.2.6 Participation in any prior DHEA study or administration of DHEA within the past 3 months.
- 4.2.7 Use of investigational agents within the longer of 30 days or 10 half-lives of the agent.
- 4.2.8 Any condition which in the investigator's or sponsor's opinion is sufficient to prevent adequate compliance with the study or likely to confuse follow-up evaluation (e.g., alcoholism, drug addiction, acute withdrawal from chemical dependency, psychiatric disease).
- 4.2.9 Patient requires treatment/medication prohibited by protocol.
- 4.2.10 Any serious EKG abnormality as determined by the Investigator.
- 4.2.11 Patients who are pregnant.
- 4.2.12 Patients who are breast feeding.

#### 4.3 Qualification for study

The Screening Visit begins the qualification period (no more than 10 days should elapse between Screening and Qualifying Visits). Once written informed consent is obtained, patients will have laboratory evaluations performed. Inclusion/Exclusion Criteria will be reviewed and the ACR Criteria for SLE diagnosis will be completed.

Within 10 days of the Screening Visit, patients will have a Qualifying Visit. At this visit, lab evaluations will be reviewed and no changes in doses of azathioprine,

methotrexate, or Plaquenil are allowed after the Screening Visit unless indicated for toxicity. A *serum pregnancy test* by a central laboratory will be performed and after completing evaluations for the Qualifying Visit, patients meeting Inclusion/Exclusion Criteria will be dispensed a 13 week supply of study medication and scheduled to return in 13 weeks for Visit 1.

#### 4.4 Assignment of Treatment

Patients who complete the qualifying period and meet the Inclusion/Exclusion Criteria will be randomized to receive double-blind, either GL701 200 mg/day or placebo. Each patient will take 4 capsules daily throughout the double-blind dosing period. Containers dispensed at each visit will contain sufficient study medication for a 13 week dosing period.

Patients will be instructed to take 4 capsules with water once daily at the same time each morning, and instructed on the importance of complying with the dosing regimen.

#### 4.5 Treatment Period

Patients will be treated for 52 weeks, and required to visit the clinic every 13 weeks. At each visit the patient will be asked to complete the Patient Self Assessment (VAS), the SF-36 Health Survey and the Krupp Fatigue Severity Score. Safety information will be collected and all remaining visit activities will be performed. A 13 week supply of GL701 200 mg/day or placebo will be dispensed at the Qualifying Visit, Visit 1 (Week 13), Visit 2 (Week 26) and Visit 3 (Week 39).

Temporary discontinuation of study drugs should be prospectively discussed with the Genelabs Monitor.

#### 4.6 Concomitant Medications

4.6.1 No other investigational medications may be taken during the study.

4.6.2 No immunosuppressive agent, except azathioprine or methotrexate, may be taken during the study.

4.6.3 No changes from baseline (study entry) are allowed for dosages of Plaquenil (hydroxychloroquine), methotrexate, or azathioprine except for documented drug toxicity. Patients receiving methotrexate must receive 1 mg folate daily as vitamin supplementation.

4.6.4 Prednisone dose in patients receiving alternate day therapy will be the mean prednisone dose.

- 4.6.5 All efforts should be made to maintain prednisone at baseline dose level. Daily prednisone dosage can be increased up to 10 mg over baseline dosage within the first two months of participation only (see 11.3.4 for stress doses). Throughout the remainder of the study, daily prednisone dosage can be increased up to only 5 mg greater than the baseline dose and only for up to 2 consecutive months. Throughout the trial, all reasonable attempts should be made to return the prednisone dose to the baseline in patients who have required increased prednisone dosing. Other changes, with the exception of those required under emergency care, will require authorization from the sponsor.
- 4.6.6 Changes in NSAIDs (by dosage or NSAID, e.g., ibuprofen to naproxen) may be made, but only if medically required and approved by the treating physician.
- 4.6.7 Patients who require treatment with stress doses of steroids must be preapproved by the sponsor except in case of life-threatening emergency.
- 4.6.8 Pulse intravenous steroids (e.g. methylprednisolone) should be listed as concomitant medications for patients who require short-term pulse therapy with steroids.
- 4.6.9 Patients who develop acneiform dermatitis should be treated with the approved products containing the following active agents: Benzoyl peroxide, metronidazole, topical tetracycline. In more severe cases, oral erythromycin may be prescribed.
- 4.6.10 All use and changes in concomitant medications (including addition or discontinuation of medications) will be recorded, including those occurring between scheduled protocol visits.

## 5. STUDY DRUG FORMULATION AND PACKAGING

### 5.1 GL701

- 5.1.1 GL701 is Genelabs' formulated version of dehydroepiandrosterone (DHEA).
- 5.1.2 Study medication will be supplied by Genelabs. All study medications are identical in appearance (opaque, white, gelatin capsules). Study medication is to be stored under limited access at room temperature, 59-86°F in a dry environment.

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

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

- 5.1.3 Drug Packaging: Study medication will be packaged in a blinded manner in plastic bottles containing 400 capsules (**Containers are not child proof, precautionary storage measures must be taken to keep study medication out of the reach of children**). One bottle will be dispensed at each Dosing Visit. An additional 10 day supply of capsules will be included in each bottle in case of spillage or damage to a capsule. The bottles will be labeled individually with the following information:

- Patient #: \_\_\_\_\_ Patient Initials \_\_\_\_\_
- Date Dispensed: \_\_\_\_\_
- Visit # \_\_\_\_\_ Week # \_\_\_\_\_
- Contents: 400 Capsules
- Protocol #: GL95-02
- Directions for Use: Take four (4) capsules once daily at the same time each day
- Container is not child proof - keep out of the reach of children
- Caution: New Drug - Limited by Federal (United States) Law to Investigational Use
- Store at room temperature (59° - 86°F) in a dry environment
- GENELABS TECHNOLOGIES, INC. REDWOOD CITY, CA 94063

- 5.1.4 The study medication label will have a portion permanently affixed to the bottle, and a tear-off portion to keep in the pharmacy. The Investigator or his designee will write the date dispensed and the patient initials on both the attached and tear-off label. The tear-off portion of the label must be removed and attached to the appropriate case report form prior to handing the container to the patient.

In the event of an emergency that requires 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 should be notified immediately

if any patient's treatment is unblinded and unblinding should be noted in the case report form as well as reasons and authorization for unblinding.

- 5.1.5 Patients will take four capsules, once daily at the same time each morning. All medication supplied is to be accounted for on the Drug Accountability Record. Any used or unused supplies including empty bottles must be returned to Genelabs. This medication is limited to investigational use and can only be administered to patients who meet the entry criteria of this protocol under the direction of those identified on the FDA Form 1572.

## 6. STUDY ACTIVITIES

Every effort should be made to consistently schedule each patient's visits at approximately the same time of day for each visit. If possible, the patient should be interviewed and examined by the same physician and/or coordinator throughout the duration of the study.

Patients who discontinue study medications for any reason will continue to be evaluated at scheduled visits (i.e. 13, 26, 39, 52 weeks) including assessment of SLAM and SLEDAI scores and adverse events. Additionally, an assessment of adverse events will be conducted by telephone 6 weeks following discontinuation of study medications. All visits should be scheduled relative to the baseline visit.

Patients should be contacted prior to each dosing visit and reminded to:

- Begin collecting the 24 hour urine specimen one day prior to the dosing visit.
- To fast, with nothing to eat or drink (water permitted) unless contraindicated (e.g., diabetes) for 8 hours prior to the visit.
- Not to dose with study medication until after laboratory procedures have been performed on days when required blood tests are taken (this may coincide with scheduled Study Visit days)
- To return all study medication including empty containers.

### 6.1 Screening Visit (Conducted within 10 days of Qualifying Visit)

- 6.1.1 The patient will be provided and review a patient information sheet and will sign an IRB approved Consent Form. Fasting blood and urine will be collected (see 8.1.1).

- 6.1.2 Demography, Medications (past treatment history including the use of glucocorticoids and immunosuppressive agents) and Medical History including any significant prior organ system involvement.
- 6.1.3 ACR Criteria for diagnosis of SLE.
- 6.1.4 Physical exam including vital signs (sitting blood pressure and pulse from the nondominant arm), weight and height.
- 6.1.5 SLICC Damage Index by physician.
- 6.1.6 SLAM Determination by physician.
- 6.1.7 SLEDAI Determination by physician.
- 6.1.8 KFSS by patient
- 6.1.9 SF-36 by Patient
- 6.1.10 Global Disease Activity Assessment using a 10 cm VAS scale by patient and physician. Physicians and patients will not be shown prior VAS.
- 6.1.11 Central Lab: Fasting blood and urine sample, serum pregnancy test, and 24 hour urine collection (see Section 8).  
  
(Patients should be fasting for 8 hours, nothing to eat or drink until after blood and urine specimens have been obtained unless contraindicated) (e.g., diabetes mellitus).
- 6.1.12 Local Lab: Blood sample for Westergren Erythrocyte Sedimentation Rate (ESR).
- 6.1.13 Genelabs: Serum sample for DHEA-S. 3-4 ml total volume of cell free serum is required. Obtain this sample at the Screening Visit prior to study drug administration (see Appendix 15.5). If the sample is not taken at the Screening Visit, it may also be obtained at the Qualifying Visit.
- 6.1.14 Obtain a 12 lead electrocardiogram (EKG). (May be conducted within 2 weeks prior to Screening exam and procedures).
- 6.1.15 Schedule patient for Qualifying Visit within 10 days of this visit. Laboratory results from Covance must be received for the Qualifying Visit to occur. This will allow you to complete the SLEDAI and SLAM scores for the patient.

## 6.2 Qualifying Visit (Initial Dosing Visit with Qualification) - Week 0

(This should occur as soon as possible after Screening evaluations but must occur within 10 days of Screening Visit). You must have received laboratory results from Covance for the Qualifying Visit to occur. This will allow you to complete the SLAM and SLEDAI scores for the patient. Patient will be assigned a Patient Identification Number upon dispensing of study drug at this visit.

- 6.2.1 Central Lab: Serum pregnancy test
- 6.2.2 Confirm that all eligibility criteria are met, including laboratory and EKG assessments conducted post Screening Visit (see Inclusion Criteria section 4.1 and Exclusion Criteria section 4.2).
- 6.2.3 SF-36 and Krupp Fatigue Severity Scoring by patient.
- 6.2.4 Concomitant Medication Review.
- 6.2.5 Adverse Event Assessment.
- 6.2.6 SLEDAI scoring by physician.
- 6.2.7 SLAM scoring by physician.
- 6.2.8 Global Disease Activity Assessment using a 10 cm VAS scale by patient and physician. Physicians and patients will not be shown prior VAS.
- 6.2.9 If patient qualifies at this visit based on laboratory and clinical evaluations, the patient will be enrolled and a randomization code assigned.
- 6.2.10 Assign randomization number for patient from drug supplies.

Study medications are numbered sequentially with respective randomization numbers. Explain study medication dosing and packaging. Patient will begin taking study medication the morning following this visit.

Patient should be reminded not to take study medication the morning of the next visit. Remind patient to bring back all remaining medication, including any empty containers.

- 6.2.11 Schedule patient for laboratory evaluations the day of the next Dosing Visit (Visit 1, Week 13).
  - 6.2.12 Dispense container for a 24 hour urine specimen (to be collected 24 hours prior to next scheduled visit at Week 13, see Section 8.1 for instructions to patient).
  - 6.2.13 At selected sites, some patients who have received prednisone for at least 6 months will undergo dual energy X-ray absorptiometry (DEXA) scanning of the lumbar vertebrae (either L1 or L2 - L4) and the nondominant proximal femur (neck, Ward's triangle, trochanter, and intertrochanteric region) Posterior-anterior (PA) scans will be obtained within 10 days of baseline.
- 6.3 Quarterly Dosing Visits 1, 2, and 3 (Weeks 13, 26, and 39 ± 2 weeks)**
- 6.3.1 Reminder: All visits should be scheduled relative to the baseline visit in order to maintain the 52 week schedule. Schedule patient for laboratory evaluations the day of all Dosing Visits. Patients should be reminded not to take study medication the morning of these visits until after laboratory specimens are drawn and assessments completed.
  - 6.3.2 Adverse Event Assessment.
  - 6.3.3 Concomitant Medication Review.
  - 6.3.4 Drug Dispensing Log.
  - 6.3.5 Physical exam, including vital signs (sitting blood pressure and pulse from the nondominant arm), weight.
  - 6.3.6 SLEDAI scoring by physician.
  - 6.3.7 SLAM scoring by physician.
  - 6.3.8 Global Disease Activity Assessment using a 10 cm VAS scale by patient and physician. Physicians and patients will not be shown prior VAS.
  - 6.3.9 SF-36 and Krupp Fatigue Severity Scoring by patient.
  - 6.3.10 Central Lab: Fasting blood and urine sample, serum pregnancy test, and 24 hour urine collection (see Section 8).

*(Patients should be fasting for 8 hours, nothing to eat or drink until after blood and urine specimens have been obtained unless contraindicated) (e.g., diabetes mellitus).*

- 6.3.11 Local Lab: Blood sample for Westergren Erythrocyte Sedimentation Rate (ESR).
- 6.3.12 Genelabs: Serum sample for DHEA-S. 3-4 ml total volume of cell free serum is required (see Appendix 15.5) **Visit 1 only.**
- 6.3.13 Dispense study medication. **Remind patient to return all remaining medication, including empty containers.**
- 6.3.14 Dispense container for the 24 hour urine specimen (to be returned at the next visit).

#### **6.4 Completion Visit or Early Termination Visit (Week 52, or as appropriate)**

*(Patients should be fasting, nothing to eat or drink until after blood and urine specimens have been obtained unless contraindicated) (e.g., diabetes mellitus).*  
**Remind patients not to take study medication the morning of this visit.**

- 6.4.1 Central Lab: Fasting blood and urine sample and serum pregnancy test.

- 6.4.1.1 **Hormone levels performed by Covance: The patient is requested to withhold hormone replacement medication (HRT) on the day of the visit until after the following blood sample has been collected:**

- Serum levels of estrone

**(The above laboratory test will be analyzed by COVANCE, which will provide all supplies for the above listed blood sample.)**

- 6.4.2 Local Lab: Blood sample for Westergren Erythrocyte Sedimentation Rate (ESR).
- 6.4.3 Genelabs: Baseline serum sample for DHEA-S. 3-4 ml total volume of cell free serum is required (see Appendix 15.5).
- 6.4.4 SLEDAI scoring by physician.

- 6.4.5 SLAM scoring by physician.
- 6.4.6 SLICC Damage Index by physician.
- 6.4.7 Global Disease Activity Assessment using a 10 cm VAS scale by patient and physician. Physicians and patients will not be shown prior VAS.
- 6.4.8 SF-36 and Krupp Fatigue Severity Scoring by patient.
- 6.4.9 Physical exam including vital signs and weight. Blood pressure will be taken on the non-dominant arm with the patient seated for at least three (3) minutes.
- 6.4.10 EKG.
- 6.4.11 Adverse Event Assessment.
- 6.4.12 Concomitant Medication Review.
- 6.4.13 Drug Dispensing Log.
- 6.4.14 Treatment Completion / Early Termination forms.
- 6.4.15 Verify all medication including empty containers have been returned by the patient.
- 6.4.16 (Selected investigator sites): Repeat DEXA scanning of the lumbar vertebrae (either L1 or L2 - L4) and the nondominant proximal femur (neck, Ward's Triangle, trochanter, and intertrochanteric region) if the patient has been treated *with study drug, in the study, for at least 6 months*.
- 6.4.17 Diagnostic test for all postmenopausal women:
  - **Mammography**: This test is required on all postmenopausal patients, unless it has been performed within 12 months of the visit and records are available.
- 6.4.18 Diagnostic tests for all postmenopausal women with an intact uterus (patients who have not had a hysterectomy):

- 6.4.18.1 **Transvaginal Ultrasound**: This test is performed to establish a baseline measurement of endometrial thickness. (Appendix 15.9)
- 6.4.18.2 **Endometrial Biopsy**: Patients should undergo this procedure if the transvaginal ultrasound showed an endometrial thickness of  $\geq 5$ mm. (Appendix 15.9)

#### 6.4.19 Obtain Written Informed Consent

### 6.5 Follow-up for All Patients (6 Weeks Post Completion or Early Termination)

All patients are to undergo follow-up as below:

- 6.5.1 Patients who complete the full 52 weeks of treatment with study drug will be eligible to receive GL701 in an open label safety study.
- 6.5.2 Any eligible patient who completes the full 52 weeks course of treatment with study drug but chooses not to participate in the open label study will also be contacted by telephone 6 weeks following the Completion Visit, for evaluation of possible delayed adverse events.
- 6.5.3 Patients who discontinue study medications for any reason will continue to be evaluated at scheduled visits (i.e. 13, 26, 39, 52 weeks) including assessment of SLAM, VAS (patient and physician) KFSS, SF-36, SLEDAI scores and adverse events. It is not necessary to perform an EKG at Week 52 for patients who previously discontinued study medication and underwent all completion/Early Termination procedures. Additionally, an assessment of adverse events will be conducted by telephone 6 weeks following discontinuation of study medications.  
  
Patients who discontinue the study prior to 52 weeks for any reason will undergo all Completion/Early Termination Visit procedures and will be contacted 6 weeks following discontinuation of study medication, by telephone, for evaluation of concomitant medications and possible delayed adverse events.
- 6.5.4 All adverse events will be followed until resolution or explanation of event.
- 6.5.5 Any patient who becomes pregnant during the study will be discontinued from study medications but will be followed until delivery. Data concerning fetal outcome will be collected.

- 6.5.6 All remaining evaluations will be conducted as originally scheduled on patients who have prematurely discontinued study medications.

## 6.6 Conditions for Early Termination from Study Medications

Patients who terminate treatment early will be classified into one of the following categories:

Early withdrawal due to:

- a) Safety/efficacy reasons
- b) Administrative reasons (e.g. lost to follow-up, moved out of the area, etc.)

Every effort will be made to continue treatment medications, but if study drug administration is suspended, every effort will be made to continue all evaluations for up to the 1 year and follow-up period as specified by protocol. When study drug administration or study participation is discontinued, reasons will be recorded on the case report form.

## 6.7 Post-Completion Visit

- 6.7.1 This section applies to all post-menopausal women who have not undergone a hysterectomy (indicating an intact uterus) and who completed the GL95-02 protocol within the last six months of this visit.
- 6.7.2 Contact the patient by telephone or in writing as soon as feasible to schedule this visit and discuss the content of this amendment.
- 6.7.3 Obtain written consent (revised to include Amendment #2)
- 6.7.4 Transvaginal Ultrasound: This test is performed to establish a baseline measurement of endometrial width. (Appendix 15.9)
- 6.7.5 Endometrial Biopsy: Patients should undergo this procedure if the transvaginal ultrasound showed an endometrial width of  $\geq 5$ mm. (Appendix 15.9)
- 6.7.6 Hormone levels performed by Covance: *The patient is requested to withhold hormone replacement medication (HRT) on the day of the visit, until after the following blood sample has been collected:*

#### 6.7.6.1 Serum levels of estrone

(The above laboratory tests will be analyzed by COVANCE, which will provide all supplies for the above listed blood samples.)

#### 6.7.7 Concomitant Medication Review

### 7. CLINICAL EFFICACY EVALUATIONS

Clinical efficacy evaluations will include disease severity (SLAM and SLEDAI scores), constitutional symptoms (patient VAS and Krupp Fatigue Severity Score), as well as use of new or increased concomitant medications, appearance of new or progressive organ disease, serious drug toxicity, administration of new or increased cytotoxic drugs, and increments in prednisone (or steroid equivalent) dosage.

### 8. LABORATORY EVALUATIONS AND DEXA SCANS

#### Central Laboratory (Covance)

Blood and urine specimens will be obtained prior to dosing, for the following laboratory tests at Visits Screen, Week 13, Week 26, Week 39 and Completion/Early Termination unless otherwise indicated.

Screening and Completion/Early Termination labs should be obtained following an overnight fast. Laboratory results must be received from Covance for patient qualification, allowing the investigator to complete the SLAM and SLEDAI scores for the patient. Copies of results of all laboratory tests should be filed with the Investigator's copy of the patient's case report forms.

Lab evaluations occurring at Screening, Week 13, Week 26, Week 39 and at Completion/Early Termination should include the following (See Appendix 15.6):

- Serum Chemistry including: Total Bilirubin, Alk Phos, AST (SGOT), ALT (SGPT), LDH, Urea Nitrogen, Creatinine, Glucose, Uric Acid, Calcium, Phosphorus, Total Protein, Albumin
- Lipids including: Total cholesterol, triglycerides, LDL-C and HDL-C.
- Serum pregnancy test (beta hcG) at Screening and at all visits for women of child bearing potential.
- CBC with platelet count.
- Urinalysis with microscopic analysis.
- 24 hour urine for creatinine clearance and protein quantitation.

- Anti-nuclear antibodies (ANA).\*
- Anti-ds DNA.
- Anti-cardiolipin antibodies\*\*
- Complement Levels: C3, C4.
- Serum Levels of 17 $\beta$  estradiol, total testosterone.\*\*
- Serum levels of FSH (LH\*)
- Prolactin levels\*\*
- Steroid hormone binding globulin\*\*
- glycosylated hemoglobin (HBA<sub>1</sub>C)\*\*

(\* = Baseline Only, \*\* = Baseline and Termination Only)

All of the above laboratory tests will be analyzed by Covance, who will provide all supplies for the above listed blood and urine samples. All specimens should be sent by designated overnight courier.

Reports of results (serum levels of 17 $\beta$  estradiol and testosterone will be blinded) will be mailed from Covance to the respective investigator and directly to Genelabs. If there are any problems or significant findings, Covance will contact the Investigator immediately by phone. Abnormal lab results which are clinically significant should be reported on the Adverse Events Form. Abnormal results which are not clinically significant or requested to be repeated, are to be initialed and noted on the "Comments" Form.

### 8.1 24 Hour Urine

8.1.1 Patients must collect the 24 hour urine specimens within 48 hours of the serum specimens in order to accurately calculate the creatinine clearance.

8.1.2 Containers for the 24 hour urine specimens should be provided to the patient at each visit to be returned at the following visit. For the Screening Visit specimen, patients will need to be seen prior to the actual visit, sign the Informed Consent and be dispensed the container. Patients will be instructed on how to collect and store a 24 hour urine specimen:

Patients will be instructed that on the day of collection, they should discard the first morning urine void, and begin the collection after this void. All urine will be collected for the next 24 hours so that the morning void on the second day is the final collection. Patients will be asked to record the time in which the collection commenced and concluded.

Patients will store the 24 hour urine collection either, under refrigeration ( $\geq 4^{\circ}\text{C}$  and  $< 10^{\circ}\text{C}$ ) or in a cool dry environment.

## 8.2 Local Lab

Westergren Erythrocyte Sedimentation Rate to be analyzed by a local laboratory.

## 8.3 Genelabs

DHEA Serum Samples are to be shipped to Genelabs for analysis (see Appendix 15.5).

## 8.4 PA Dual Energy X-ray Absorptiometry (DEXA) Scans

At selected investigational sites, patients who qualify for entry and have been treated with glucocorticoids for at least six (6) months will undergo PA Dual Energy X-ray Absorptiometry (DEXA) scans of the lumbar spine and nondominant proximal femur at baseline and one year (Termination) Visits (See Appendix 15.8).

## 9. ADVERSE EVENTS

### 9.1 Adverse Event Reporting

An adverse event occurring in this study, whether or not deemed to be causally associated with the study medication, is defined as:

An undesirable and unintended clinical occurrence or a laboratory result that is related in time but is not necessarily caused by the administration of a drug, for example:

1. An abnormal change in physical signs or symptoms
2. An abnormal result of a laboratory test that results in a change in concomitant medication or results in interruption or withdrawal of the (study) medication
3. Any change in the result of a laboratory test that the investigator judges clinically significant

9.1.2 Adverse events should be elicited by indirect questioning using a non-leading question such as, "Since your last visit, is anything bothering you?"

9.1.3 Follow-up of all adverse events will be continued until the overall clinical outcome has been explained or resolved.

9.1.4 All adverse events throughout the course of the study will be reported on an "Adverse Event" case report form. Adverse event reports should describe the event, date of onset, frequency (e.g., constant, intermittent), duration, severity (e.g., mild, moderate, severe), and the investigator's opinion of the relationship to the study drug (e.g., probably related, possibly related, probably not related). In addition, the action taken (e.g., none or study drug discontinued) should be recorded. The following definitions for rating severity of adverse events may be used:

Mild	Subject is aware of signs or symptoms but can tolerate them easily. Signs or symptoms are of minor irritant type; there is no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.
Moderate	Signs or symptoms cause enough discomfort to interfere with usual activities.
Severe	Signs or symptoms are incapacitating; subject is unable to do work or usual activities; signs or symptoms may be of systemic nature or require medical evaluation and/or treatment.

## 9.2 Serious Adverse Events

9.2.1 The investigator must decide whether each event meets the definition of a serious adverse event. A serious adverse event is defined as *any event* that:

1. Is fatal
2. Is life-threatening (i.e., the patient is at immediate risk of death from the event as it occurred)
3. Results in permanent or significant disability
4. Results in a new or prolongs a hospitalization
5. Is a congenital anomaly

6. Requires medical or surgical intervention to avoid permanent impairment/damage

9.2.2 All other events that are considered medically serious by the investigator must be reported within 24 hours to Genelabs as well.

**ALL SERIOUS ADVERSE EVENTS (WHETHER OR NOT CONSIDERED DRUG RELATED) INCLUDING ALL DEATHS** must be reported immediately (within 24 hours) by telephone to the Genelabs medical monitor or clinical research associate (CRA), confirmed in writing, and recorded on the "Adverse Event" case report form. (Addresses and telephone numbers of Genelabs personnel are on the cover page of this protocol.)

9.2.3 Reports relating to the patient's subsequent medical course must be submitted to Genelabs until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Additionally, if the investigator learns of any serious adverse event that occurred after the follow-up period, for which there is a reasonable possibility of study drug relationship, that event should be reported to the Genelabs medical monitor immediately. It is the responsibility of the investigator to notify the IRB of all serious adverse events.

9.2.4 All serious adverse events should be reported according to the above procedure regardless of relationship to use of the trial medication, the nature of the trial medication, and whether the serious adverse event was expected or unexpected.

### **9.3 Serious, Unexpected, Drug-Related Adverse Events**

During clinical trials, data on serious, unexpected, drug-related adverse events are collected on an ongoing basis by Genelabs and are disseminated to relevant investigators and regulatory agencies within 10 days of the original notification to Genelabs.

Such reports constitute addenda to the Investigator's Brochure. It is the investigator's responsibility to file such addenda with the Investigator's Brochure. The investigator is also responsible for notifying the relevant IRB of such new data.

## **10. STUDY ADMINISTRATION**

### **10.1 Institutional Review Board**

- 10.1.1 This study must have the approval of a properly constituted Institutional Review Board (IRB) or Committee recognized by the FDA for approving clinical studies. Each Investigator will advise his/her IRB of the progress of this study at least once yearly and will obtain approval to continue the study.

Before investigational drug is shipped to the clinical study site, 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.

- 10.1.2 All advertisements must be approved by Genelabs and the IRB.
- 10.1.3 Any amendments to the protocol, as well as consent form changes, will be submitted to the IRB and written approval obtained prior to implementation.
- 10.1.4 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.

## 10.2 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 and any amendments to the consent must be approved by the Institutional Review Board prior to implementation. 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 shipment of study drug and initiation of the study.

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

The study will be explained to the patients in lay language. A copy of the signed Informed Consent Form (including amended consents) must be given to the patient prior to study participation. The Investigator must keep each patient's signed consent form(s) on file and readily available for review by the Study Monitor and for FDA inspection at any time.

### 10.3 Source Documentation

- 10.3.1 Regulatory agencies require that information be maintained in the patient's medical records to corroborate data collected on the case report forms.
- 10.3.2 Genelabs will require access to the patient's original medical records to corroborate data collected on the case report forms.

### 10.4 Drug Accountability

Each shipment of study drug 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, as well as the lot and protocol number for the drug. All shipment contents should be verified against the shipping forms. Any discrepancies, 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, Inc.  
8000 E. Commerce Parkway  
Mount Laurel, NJ 08054

Study drug must be stored in a secure, controlled or limited access, locked area at room temperature (59° - 86°F) or in a dry environment

Drug Accountability Records should cover receipts, dispensing, and return of study drug supplies. Separate inventory records should be kept for each protocol performed at the site. Drug is labeled with a specific protocol 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:

The identification number of the subject to whom the medication is dispensed.

The date study drug is dispensed and quantity dispensed.

The date study drug or it's empty container is returned and quantity returned.

Inventory records must be readily available for inspection by the CRA and are open to FDA inspection at any time.

GL701 drug supply will be packaged in a blinded manner and shipped from Simirex Inc. to the sites. Only authorized personnel designated by the Principal Investigator (FDA Form 1572) should be able to administer the drug.

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 bottles and lot numbers being returned on the Patient Drug Inventory Record, 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 for each subject, including all used bottles, have been returned and that no supplies remain in the Investigator's possession. If all study drug supplies are not returned, the Investigator must include an explanation and document that all attempts to have supplies returned have failed. A copy of the Patient Drug Inventory Records will be collected by the CRA.

Return Used and Unused Bottles To:

*Drug Development*  
Genelabs Technologies, Inc.  
505 Penobscot Drive  
Redwood City, CA 94063  
(650) 369-9500 ext. 465

## 10.5 Record Retention

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

- 10.5.1 Case Report Forms – must be legible, accurate and up to date with copies of all corrections.
- 10.5.2 Patient Files – confirm data entered in the Case Report Forms including laboratory data, EKG interpretations, patient histories, treatment regimens, physical examinations, concomitant medications, and any adverse events.

- 10.5.3 Patient Non-Qualifier Log – record the reason a patient was screened for study participation and found to be ineligible.
- 10.5.4 Patient Drug Inventory Record – record the total amount of study drug dispensed to and returned from the patient (see section 8.3). This information must agree with the information entered in the Case Report Forms.
- 10.5.5 Copies of all Clinical Supplies Shipment Forms must be signed and dated.
- 10.5.6 Informed Consent Forms – signed consent forms from each patient must be available and verified for proper documentation and approval.
- 10.5.7 Informed Consent Log - record the date, initials, and protocol number (if applicable) of any patient who either signed an Informed Consent form or offered other documentation giving consent.

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

## 10.6 Case Report Forms

Data will be recorded on Case Report Forms provided by Genelabs. 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 Coordinator or Investigator or Pharmacist (for Drug Accountability or FR94 Forms). Corrected copies of CRFs will be filed with the corresponding original.

Case Report Forms will be completed and collected on a timely basis. Investigators may be requested to send completed Adverse Event and Concomitant Medication forms to Genelabs by facsimile. The original Case Report Forms will remain at the site until collected by the CRA.

## 10.7 Monitoring the Study

Individual sites will be monitored at appropriate intervals to assure satisfactory enrollment, data recording, and adherence to the protocol. The frequency of monitoring of an individual clinical site may vary depending on its enrollment rate and the quality of data collected. The Investigator and staff are expected to cooperate with the CRA at

each site visit and provide all relevant study documentation upon request for review. In addition to regular visits, each site may be monitored by phone and fax to keep abreast of patient status and to answer questions.

## 10.8 Study Amendment

With concurrence of the Investigator, if the protocol needs to be amended, the Sponsor will provide the Investigator with protocol amendment documents. 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. All deviations from the prescribed protocol procedures must be approved in writing by the Sponsor.

## 10.9 Final Study Report

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

## 11. TEST OF SUCCESS: CRITERIA

### 11.1 Primary Efficacy Variable

The primary efficacy variable in this study is the proportion of patients who are responders. All patients who receive study drug by randomized allocation will be evaluated.

A responder is defined as a patient who satisfies the following conditions:

- a) Improvement or stabilization in all disease activity (i.e. SLAM, SLEDAI) and constitutional symptom assessments (i.e., KFSS, Patient VAS).

For each of the disease activity variables or constitutional symptom variables, the value of interest for each patient will be the difference between the mean of the two baseline values and the mean of all values obtained during on-treatment scheduled visits (e.g., 13, 26, 39 and 52 week visits or Early Termination).

For each patient, on-treatment visits are defined as the visits (planned or Early Termination) before termination of study drugs.

- b) A patient must not have (as collected in the patient CRFs) clinical deterioration as described in Section 11.3.

#### 11.1.1 Covariables

Baseline variables, including race, absence/presence of cytotoxic drug therapy, absence/presence of prednisone use, SLAM, SLEDAI, KFSS, patient's VAS and/or menopausal status, will be assessed for inclusion in the primary analysis whenever possible.

#### 11.2 Secondary Efficacy Variables

- a. For each of the following variables, the value of interest will be the group means for the difference between the mean of the two baseline observations and the mean of all scheduled on-treatment visits (e.g., 13, 26, 39 and 52 week visits). All randomized patients will be included in the evaluation.

- SLEDAI
- SLAM
- Patient's VAS
- KFSS
- Physician's VAS
- SF-36
- Prescribed prednisone (or equivalent) dose

- b. For each of the following variables, the value of interest will be the group means for the difference between the mean of the two baseline observations and the value at the 52 week visit (for those patients who complete the study, with or without early discontinuation of study medication).

- SLAM
- SLEDAI
- KFSS
- Patient's VAS
- Prescribed prednisone (or equivalent) dose

- c. Time to clinical deterioration

- d. DEXA scan summaries

#### 11.3 Clinical Deterioration

Clinical deterioration may occur as a result of new onset of toxicity associated with lupus therapy, serious new or progressive lupus-related conditions, or requirement for unacceptable increase in immunosuppressive or cytotoxic therapy for lupus while the patient is receiving study drug.

The occurrence of clinical deterioration and its date will be determined in a blinded manner after a patient has completed all study activities.

- 11.3.1 The following conditions will be considered as serious drug toxicity attributable to study drug or other lupus therapy if they occur during study drug treatment or within 6 weeks post discontinuation of study drug treatment:

New onset diabetes mellitus (defined as diabetes requiring drug therapy for  $\geq 3$  months)

New gastric or duodenal ulcer not due to *Helicobacter pylori* requiring hospitalization or transfusion

New onset hypertension requiring drug therapy  $\geq 3$  months

New myocardial infarction (by EKG or enzymatic criteria)

New steroid myopathy

New elevation in serum transaminases AST, ALT to  $\geq 8$  times the upper limit of normal or a single measurement  $\geq 3$  times the upper limit of normal on multiple measurements over 3 months

New fracture and/or vertebral collapse due to osteoporosis.

- 11.3.2 The following definitions will apply to major new or progressive organ disease, assessed by the treating physician as attributable to lupus or its treatment and occurring during study drug treatment or within 6 weeks post discontinuation of study drug treatment:

**CNS:** CVA, transverse myelitis, retinal vascular occlusion, new onset of psychosis  $\geq 3$  months, new onset of seizures refractory to therapy for at least three months.

**Renal:** New onset of end stage renal disease or loss of renal function that requires dialysis for  $\geq 3$  months.

**Pulmonary:** New or worsened pulmonary hypertension and/or interstitial lung disease with reduction in diffusion capacity, mean pulmonary artery pressure and/or dyspnea at rest (NYHA Class IV).

**Cardiovascular:** Pericarditis refractory to treatment for  $\geq 3$  months or that requires pericardiectomy; cardiomyopathy refractory to therapy for  $\geq 3$  months with hemodynamic compromise (decreased cardiac index, left ventricular ejection fraction and/or dyspnea at rest) and/or refractory arrhythmia.

**Gastrointestinal:** Ischemic bowel disease that requires bowel resection.

**Vasculitis:** Vasculitis that results in infarction (excluding vasculitides described under other organ systems).

**Hematologic:** Thrombocytopenia that results in clinically significant hemorrhage with sequelae which do not resolve for  $\geq 3$  months; persistent leukopenia ( $WBC \leq 1,500$ ) that results in recurrent infections without improvement in incidence of recurrent infections for  $\geq 3$  months.

11.3.3 Increase in doses of concomitant methotrexate, or azathioprine, or institution of new therapy with cytotoxic or immunosuppressive agents (methotrexate, azathioprine, cyclophosphamide, or cyclosporine) at any time during study drug treatment or within 6 weeks post discontinuation of study drug treatment.

11.3.4 Except for stress doses<sup>4</sup>, daily prescribed prednisone dosage has exceeded 10 mg/day over baseline dosage within the first 2 months of participation or, through the remainder of the study, daily prednisone dose has increased to more than 5 mg/day over daily baseline dose for  $\geq 2$  consecutive months (See Section 4.6.4 for alternate day prednisone dosing).

## 12. STATISTICAL CONSIDERATIONS

### 12.1 Sample Size Determination

Since there is no prior information regarding the responder rates, using the criteria given in section 11.1 in this population for both treatment groups, the sample size of 300 randomized patients is not based on statistical calculations.

### 12.2 Population

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<sup>4</sup> Stress doses of steroids are defined as acute parenteral therapy with high doses of glucocorticoids intended for the treatment of an acute, self-limited process such as surgery, severe infection or other condition which would be potentially life-threatening in a patient with secondary adrenal suppression.

All randomized patients will be analyzed in an intent-to-treat analysis. All patients who received study drug will be included in the analysis of safety.

### 12.3 Investigational Center Pooling Algorithm

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

- Step 1. If at least one study site meets the pooling criteria (fewer than 3 patients in one arm), the site with the fewest intent-to-treat patients will be pooled with the next smallest site and identified as a new study site.
- Step 2. If after creation of the new study site described in Step 1, there remains at least one study site that meets the pooling criteria, step one will be repeated.

This process will continue until no site with fewer than 3 patients in either study arm remains.

### 12.4 Primary Efficacy Analysis

The proportion of responders will be analyzed by logistic regression with treatment and trial centers as factors. Baseline variables (such as race, absence/presence of cytotoxic drug, absence/presence of prednisone use, SLAM, SLEDAI, KFSS, patient's VAS, menopausal status) which attain a 0.05 significance level for association with treatment assignment will be assessed and included in the logistic regression model whenever possible.

### 12.5 Secondary Efficacy Analyses

In each of the variables specified in Sections 11.2 a and b, the change from baseline (mean of both measurements at Screening and Qualifying Visits) will be analyzed by means of a two-way analysis of covariance model with treatment and trial center as factors and baseline as a covariate. Both treatment-by-baseline and treatment-by-center interactions will be included in the model.

The secondary efficacy variables, time to discontinuation of study drug from any cause will be analyzed by means of a Cox regression model with treatment as a factor. Time to clinical deterioration will be displayed using Kaplan-Meier Curves and analyzed by the method of Cox regression using the covariables defined above.

For each of the variables in Section 11.2b, the change from baseline at the 12 month visit will be summarized by study medication status (i.e. early discontinuation of study medication or 52 weeks of treatment with study medication).

## **12.6 Safety Variables**

The nature and frequency of adverse events will be summarized by treatment groups. Changes in laboratory values will also be summarized by treatment groups.

## **13. PUBLICATION**

### **13.1 Publication by Genelabs**

Genelabs intends to publish, in a single publication, the results of all sites participating in the evaluation of the Drug. The order of authorship of the various investigators will be based on the relative contribution by each investigator as determined by the Genelabs, Inc., Clinical Department.

### **13.2 Publication by Institution or Principal Investigator**

A draft manuscript of any publications relating to the Trial shall be submitted to Genelabs at least sixty (60) days prior to intended submission. A final copy of the manuscript shall be provided to Genelabs thirty (30) days prior to submission. In the case of presentations relating to the Trial, a manuscript of the presentation shall be submitted at least fifteen (15) days prior to the date of presentation. This requirement acknowledges Genelabs' responsibility to evaluate such publications for their accuracy and consonance with Genelabs' database as stipulated in the FDA IND regulations, to ascertain whether proprietary information (including trade secrets and patent protected materials) is being utilized and inappropriately released, to provide the investigator with information which may not have been available yet to him/her, and to provide input from co-authors, if applicable, regarding content and conclusions of the publication or presentation. In the instance where Genelabs wishes to file a patent application respecting an invention disclosed in a manuscript provided to it by the Institution, up to a ninety (90) day extension of the sixty (60) working days will be granted to Genelabs.

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**15. APPENDICES**

- 15.1 ACR Criteria for Diagnosis of Systemic Lupus Erythematosus
- 15.2 SLEDAI Score for Disease Progression
- 15.3 Systemic Lupus Activity Measure (SLAM)
- 15.4 Equivalent Dosages of Glucocorticoids
- 15.5 Procedures for Processing and Shipping GL701
- 15.6 General Clinical Safety Laboratory Evaluations
- 15.7 Procedures for DEXA Scanning
- 15.8 Schedule of Events
- 15.9 Transvaginal Ultrasound and Endometrial Biopsies

## APPENDIX 15.1 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                        | <ul style="list-style-type: none"><li>a. Pleuritis--convincing history of pleuritic pain, or rub heard by physician, or evidence of pleural effusion</li><li>b. Pericarditis--documented by EKG, or rub, or evidence of pericardial effusion</li></ul>  |
| Renal Disorder                   | <ul style="list-style-type: none"><li>a. Persistent proteinuria &gt; 0.5 g/day or &gt;3 if quantitation is not performed</li><li>b. Cellular casts--may be red cell, hemoglobin, granular, tubular or mixed.</li></ul>  |
| Neurologic metabolic electrolyte | <ul style="list-style-type: none"><li>a. Seizures-- in the absence of offending drugs or known disorder derangements (e.g. uremia, ketoacidosis, or imbalance)</li><li>b. Psychosis--in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, or electrolyte imbalance)</li></ul>                            |
| Hematologic Disorder             | <ul style="list-style-type: none"><li>a. Hemolytic anemia--with reticulocytosis</li><li>b. Leukopenia-- &lt; 4,000/mm<sup>3</sup> total on two or more occasions</li><li>c. Lymphopenia-- &lt; 1,500/mm<sup>3</sup> on two or more occasions</li><li>d. Thrombocytopenia--&lt; 100,000/mm<sup>3</sup> in the absence of offending drugs</li></ul> |

Immunologic  
Disorder

- 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 15.2 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.

Wt.	Present	Descriptor	Definition
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	Altered mental function with impaired orientation, memory or at 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 <sup>3</sup> .
1	<input type="checkbox"/>	Leukopenia	< 3,000 White blood cells/ mm <sup>3</sup> . Exclude drug causes.

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

APPENDIX 15.3 SYSTEMIC LUPUS ACTIVITY MEASURE (SLAM)

SLAM ASSESSMENT PAGE 1

VISIT: <input type="checkbox"/> Screening <input type="checkbox"/> Qualifying <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> Completion/Early Termination <input type="checkbox"/> Other WEEK: (0) (13) (26) (39) (52)					
<b>Constitutional</b>					
	ABSENT or NORMAL	MILD/MODERATE	SEVERE	NOT RECORDED	
1. Weight Loss	<input type="checkbox"/> 0	<input type="checkbox"/> 1 < 10% body weight	<input type="checkbox"/> 3 > 10%	<input type="checkbox"/>	
2. Fatigue	<input type="checkbox"/> 0	<input type="checkbox"/> 1 No limits on activity	<input type="checkbox"/> 3 Functional limitation	<input type="checkbox"/>	
3. Fever	<input type="checkbox"/> 0	<input type="checkbox"/> 1 37.5 - 38.5 °C	<input type="checkbox"/> 3 > 38.5 °C	<input type="checkbox"/>	
<b>Integument</b>					
	ABSENT	MILD	MODERATE	SEVERE	NOT RECORDED
4. Oral/nasal ulcers, or perungal erythema, malar rash, photosensitive rash, or nail fold infarct	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Present			<input type="checkbox"/>
5. Alopecia	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Hair loss with trauma	<input type="checkbox"/> 2 Spontaneous hair loss		<input type="checkbox"/>
6. Erythematous, maculopapular rash, discoid lupus, lupus profundus, or bullous lesions	<input type="checkbox"/> 0	<input type="checkbox"/> 1 < 20% total body surface (TBA)	<input type="checkbox"/> 2 20 - 50% TBA	<input type="checkbox"/> 3 > 50% TBA	<input type="checkbox"/>
7. Vasculitis (leucocytoclastic vasculitis, urticaria, palpable purpura, livedo reticularis, ulcer or panniculitis)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 < 20% (TBA)	<input type="checkbox"/> 2 20 - 50% TBA	<input type="checkbox"/> 3 > 50% TBA or necrosis	<input type="checkbox"/>
<b>Eye</b>					
	ABSENT	MILD	MODERATE	SEVERE	NOT RECORDED
8. Cytoid bodies	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Present		<input type="checkbox"/> 3 Visual acuity < 20/200	<input type="checkbox"/>
9. Hemorrhage (retinal or choroidal) or episcleritis	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Present		<input type="checkbox"/> 3 Visual acuity < 20/200	<input type="checkbox"/>
10. Papillitis or pseudotumor cerebri	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Present		<input type="checkbox"/> 3 Visual acuity < 20/200 or field out	<input type="checkbox"/>

APPENDIX 15.3 Systemic Lupus Activity Measure (SLAM) (continued)

SLAM ASSESSMENT PAGE 2

VISIT: <input type="checkbox"/> Screening <input type="checkbox"/> Qualifying <input type="checkbox"/> 1 (13) <input type="checkbox"/> 2 (26) <input type="checkbox"/> 3 (39) <input type="checkbox"/> Completion/Early Termination <input type="checkbox"/> Other					
WEEK: (0)					
<b>Reticuloendothelial</b>					
	ABSENT or NORMAL	MILD	MODERATE	SEVERE	NOT RECORDED
11. Diffuse lymphadenopathy (cervical, axillary, epitrochlear)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Shotty	<input type="checkbox"/> 2 > 1cm X 1.5cm		<input type="checkbox"/>
12. Hepato - or splenomegaly	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Palpable only with inspiration	<input type="checkbox"/> 2 Palpable without inspiration		<input type="checkbox"/>
<b>Pulmonary</b>					
	ABSENT or NORMAL	MILD	MODERATE	SEVERE	NOT RECORDED
13. Pleural effusion/pleurisy	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Shortness of breath or pain only with prompting, exam normal or near normal	<input type="checkbox"/> 2 Shortness of breath or pain with exercise, decreased breath sounds and dull lower lobe(s)	<input type="checkbox"/> 3 Shortness of breath or pain at rest, decreased breath sounds and dull middle and lower lobe(s)	<input type="checkbox"/>
14. Pneumonitis	<input type="checkbox"/> 0	<input type="checkbox"/> 1 X-ray infiltrates only	<input type="checkbox"/> 2 Shortness of breath with exercise	<input type="checkbox"/> 3 Shortness of breath at rest	<input type="checkbox"/>
<b>Cardiovascular</b>					
	ABSENT or NORMAL	MILD	MODERATE	SEVERE	NOT RECORDED
15. Raynaud's	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Present			<input type="checkbox"/>
16. Hypertension	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Diast. 90-105	<input type="checkbox"/> 2 Diast. 105-115	<input type="checkbox"/> 3 Diast. > 115	<input type="checkbox"/>
17. Carditis	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Pericarditis by EKG &/or RUB &/or effusion by echo; no sx	<input type="checkbox"/> 2 Chest pain or arrhythmia	<input type="checkbox"/> 3 Myocarditis with hemodynamic compromise &/or arrhythmia	<input type="checkbox"/>
<b>Gastrointestinal</b>					
	ABSENT or NORMAL	MILD	MODERATE	SEVERE	NOT RECORDED
18. Abdominal pain (Serositis, pancreatitis, ischemic bowel, etc.)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Complaint	<input type="checkbox"/> 2 Limiting pain	<input type="checkbox"/> 3 Peritoneal signs/ascites	<input type="checkbox"/>
<b>Neuromotor</b>					
	ABSENT or NORMAL	MILD	MODERATE	SEVERE	NOT RECORDED
19. Stroke syndrome (includes mononeuritis multiplex, transient ischemic attack (TIA), reversible ischemic neurologic deficit (RIND) cerebrovascular accident (CVA) retinal vascular thrombosis)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Single TIA	<input type="checkbox"/> 2 Multiple TIA/RIND or mononeuritis multiplex or cranial neuropathy or chorea	<input type="checkbox"/> 3 CVA/myelitis, retinal vascular occlusion	<input type="checkbox"/>
20. Seizure	<input type="checkbox"/> 0	<input type="checkbox"/> 1 1-2/month	<input type="checkbox"/> 2 > 2/month	<input type="checkbox"/> 3 Status epilepticus	<input type="checkbox"/>

APPENDIX 15.3 Systemic Lupus Activity Measure (SLAM) (continued)

SLAM ASSESSMENT PAGE 3

VISIT: <input type="checkbox"/> Screening <input type="checkbox"/> Qualifying <input type="checkbox"/> 1 (13) <input type="checkbox"/> 2 (26) <input type="checkbox"/> 3 (39) <input type="checkbox"/> Completion/Early Termination (52) <input type="checkbox"/> Other WEEK: (0)					
<b>Neuromotor (continued)</b>					
21. Cortical dysfunction	ABSENT or NORMAL <input type="checkbox"/> 0	MILD <input type="checkbox"/> 1 Mild depression/ personality disorder or cognitive deficit	MODERATE <input type="checkbox"/> 2 Δ in sensorium, severe depression, or limiting cognitive impairment	SEVERE <input type="checkbox"/> 3 Psychosis, dementia, or coma	NOT RECORDED <input type="checkbox"/>
22. Headache (including migraine equivalents)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Symptoms or transient neuro deficit	<input type="checkbox"/> 2 Interferes somewhat with normal activities	<input type="checkbox"/> 3 Incapacitating/ aseptic meningitis	<input type="checkbox"/>
23. Myalgia/myositis	<input type="checkbox"/> 0	<input type="checkbox"/> 1 Complaint	<input type="checkbox"/> 2 Limits some activity	<input type="checkbox"/> 3 Incapacitating	<input type="checkbox"/>
<b>Joints</b>					
24. Joint pain from synovitis and/or tenosynovitis	ABSENT or NORMAL <input type="checkbox"/> 0	MILD <input type="checkbox"/> 1 Arthralgia only	MODERATE <input type="checkbox"/> 2 Objective inflammation	SEVERE <input type="checkbox"/> 3 Limited function	NOT RECORDED <input type="checkbox"/>
<b>Laboratory</b>					
25. Hematocrit	NORMAL <input type="checkbox"/> 0 > 35	MILD <input type="checkbox"/> 1 30 - 35	MODERATE <input type="checkbox"/> 2 25 - 29.9	SEVERE <input type="checkbox"/> 3 < 25	UNKNOWN NOT RECORDED <input type="checkbox"/>
26. WBC	<input type="checkbox"/> 0 > 3500	<input type="checkbox"/> 1 3500 - 2000	<input type="checkbox"/> 2 2000 - 1000	<input type="checkbox"/> 3 < 1000	<input type="checkbox"/>
27. Lymphocyte count	<input type="checkbox"/> 0 1500 - 4000	<input type="checkbox"/> 1 1499 - 1000	<input type="checkbox"/> 2 999 - 500	<input type="checkbox"/> 3 < 499	<input type="checkbox"/>
28. Platelet count	<input type="checkbox"/> 0 > 150T	<input type="checkbox"/> 1 100 - 150T	<input type="checkbox"/> 2 99 - 50T	<input type="checkbox"/> 3 < 50T	<input type="checkbox"/>
29. ESR (westergren)	<input type="checkbox"/> 0 < 25	<input type="checkbox"/> 1 25 - 50	<input type="checkbox"/> 2 51 - 75	<input type="checkbox"/> 3 > 75	<input type="checkbox"/>
30. Serum creatine or creatinine clearance	<input type="checkbox"/> 0 0.5 - 1.3mg/dl or 80 - 100% CrCl	<input type="checkbox"/> 1 1.4 - 2mg/dl or 79 - 60% CrCl	<input type="checkbox"/> 2 2.1 - 4mg/dl or 30 - 60% CrCl	<input type="checkbox"/> 3 > 4mg/dl or < 30% CrCl	<input type="checkbox"/>
31. Urine sediment	<input type="checkbox"/> 0	<input type="checkbox"/> 1 > 5 RBC &/or WBC/hpf &/or 0 to 1-3 granular &/or cellular casts /hpf &/or 1-2+ proteinuria &/or < 500 mg/L 24' urine protein	<input type="checkbox"/> 2 > 10 RBC &/or WBC/hpf &/or > 3 granular &/or cellular casts/hpf &/or 3 or 4+ &/or 500 mg/L-3.5 g/L 24' urine protein	<input type="checkbox"/> 3 > 25 RBC or WBC/hpf &/or Red cell cast &/or > 4+ proteinuria &/or > 3.5 g/L 24' urine protein	<input type="checkbox"/>

**APPENDIX 15.4**                      **Equivalent Dosages of Glucocorticoids**

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

## APPENDIX 15.5 Procedures for Processing and Shipping GL701 Serum Sample Specimens for Study GL95-02

I. This procedure applies to specimen collection for serum pharmacokinetics evaluation. Specimens are taken at Screening (*or Qualifying if sample is missed at the Screening Visit*), Dosing 1 and Completion or Early Termination Visits, and are assayed and banked by Genelabs Quality Control Department.

### II. Equipment and Materials (provided by Genelabs)

1. Serum tubes, 5 mL, red top, Vacutainer, no additive, silicone coated.
2. Sample tube labels.
3. Specimen log sheets (packing list for shipment contents).
4. Safety mailer system, 3-tube, for blood specimen, includes leak-resistant foam mailer, absorbant material, waterproof tape, plastic outer bag, corrugated shipping carton, Thermosafe, Mfr. No. 473, Baxter cat.# M1062-1, or equivalent double packaging for shipping biohazard tubes.
5. Insulated polyfoam shipper, in corrugated carton.
6. Refrigerant gel packs.
7. Shipping contents label (provided).

### III. Procedure

1. Each site is to make blood draws for pharmacokinetics evaluation using serum tubes ("red tops", no anticoagulant) at Screening (*or Qualifying if sample is missed at the Screening Visit*), Dosing 1 and Completion or Early Termination visits.
2. After draws are taken, samples should be processed by each site as follows:
3. Separate serum from red cells by centrifuging each tube for 10 minutes at "1000 x g". After centrifugation, move tubes into a biohood work area. Using sterile technique, remove tube caps from the spun tubes and aspirate the cell free serum fraction using a sterile disposable pipet. Do not pick up red cells when aspirating. **Note: Be sure to start with enough drawn blood to**

yield at least 3 to 4 mL of cell free serum from each patient at collection (Approximately 7-8mL whole blood).

4. Remove the top from an unused 5 mL Red Top Vacutainer serum tube provided by Genelabs. Note: **Be sure to use only glass tubes of this type. Do not put serum into plastic tubes as analytes can absorb to plastic and cause low values.** Dispense aspirated serum into the empty 5 mL tube. Reclose the tube with the red top using sterile technique.
5. Label the 10mL tube containing serum with preprinted tube labels provided by Genelabs, **adding the date and time of last study medication to the label.** It is best to apply information to the labels prior to adhering them to the tube. Patient and study information should be hand written with indelible ink on each label by responsible site personnel.
6. **Place each specimen tube in a separate small plastic bag. The specimens should then be frozen immediately at  $\leq -20^{\circ}\text{C}$ !**
7. Each site should enclose a packing list with each shipment to identify contents. The packing list must not be placed inside the safety mailer. It should be placed inside the styrofoam shipping box which also holds the safety mailer. Be sure to protect it from the moisture of the cold pack present in the shipping box.
8. **Batch vials in freezer until ready for shipment. When ready to ship, please place the vials in the bubble-wrapped envelope (One vial per bubble-wrap) to prevent breaking. Place specimen(s) along with log sheet in the big Styrofoam box; surround the bubble-wrapped specimens with approximately 3kg of dry ice (Careful, use special gloves for handling the dry ice please). Close and secure the lid with adhesive tape. Place the DRY ICE and as well as KEEP FROZEN stickers on the outside of the box and ship to Genelabs Technologies, Inc. as before. FEDEX overnight service should be used for sites outside of the San Francisco Bay Area (airbills provided by Genelabs). Priority Express should be used for local sites (phone 415-348-6611 to arrange pick up). It is imperative that samples are not shipped on Fridays!**
9. Safety mailers and outer boxes must be labeled with warning stickers that indicate shipment of a clinical diagnostic material. **Do not use any labels other than those provided by Genelabs. Do not use any labels that indicate biohazardous materials contained inside.**

10. Containers should be addressed to Quality Control Department, Genelabs Inc., 505 Penobscot Drive., Redwood City, CA 94603, 650-369-9500.

## APPENDIX 15.6 GENERAL CLINICAL SAFETY LABORATORY EVALUATIONS

ALL OF THE THE TESTS LISTED BELOW WILL BE DONE AT SCREENING AND AT WEEKS 13, 26, 39, AND COMPLETION/EARLY TERMINATION AT THE FOLLOWING TIMES (UNLESS OTHERWISE NOTED):

<u>Serum Chemistries</u>	<u>Urinalysis</u>	<u>Complete Blood Count</u> (5 ml lavender top tube)
(10 ml serum)	Appearance	RBC
Total albumin	Specific Gravity	WBC
Alkaline Phosphatase	pH	HGB
ALT (SGPT)	Blood	HCT
AST (SGOT)	Protein	Differential
Urea nitrogen	Glucose	Platelet Count
Total Bilirubin	Ketones	
Calcium	Microscopic	
Creatinine		
Glucose		
LDH		
Phosphorus		
Total Protein		
Uric Acid		
Cholesterol		
Total cholesterol		
Total triglycerides		
LDL-cholesterol		
HDL-cholesterol		

### Specialized Tests:

- 24 hour urine for creatinine clearance and protein quantitation
- anti-nuclear antibodies (ANA)\*
- Anti-ds DNA
- Anti-cardiolipin antibodies \*\*
- Complement levels: C3, C4
- Serum levels of 17 $\beta$ -estradiol, total testosterone\*\*
- Serum levels of FSH (LH\*)
- Serum prolactin\*\*
- Steroid hormone binding globulin\*\*
- Glycosylated hemoglobin (HbA<sub>1c</sub>)\*\*
- Serum levels of estrone

(\* Baseline only; \*\* Baseline and Early Termination only)

### Instructions:

Chemistry-lipid group: 10 ml red/gray top serum separation tube. Allow blood to clot for 30 minutes. Centrifuge until clot and serum are separated by a well-formed polymer barrier. Use enclosed pipette to transfer all the serum into the 7 ml plastic vial labeled Chemistry-Lipid Group.

Estradiol/Testosterone/FSH/LH/Prolactin/Sex Hormone Binding Globulin (SHBG): 10 ml red/gray top serum separation tube. Allow blood to clot for 30 minutes. Centrifuge until clot and serum are separated by a well-formed polymer barrier. Use enclosed pipette to transfer all the serum into the 7 ml plastic vial labeled Hormones.

Complement Levels-ANA-Cardiolipin Antibodies: 10 ml red/gray top serum separation tube. Allow blood to clot for 30 minutes. Centrifuge until clot and serum are separated by a well-formed polymer barrier. Use enclosed pipette to transfer all the serum into three 7 ml plastic vials labeled Complement Levels-ANA-Cardiolipin-Frozen. FREEZE IMMEDIATELY. Ship frozen to Covance on day of collection. Refer to laboratory manual for shipping instructions.

Anti-Double Stranded DNA: 5 ml red/gray top serum separation tube. Allow blood to clot for 30 minutes. Centrifuge until clot and serum are separated by a well-formed polymer barrier. Use enclosed pipette to transfer all the serum into two 7 ml plastic vials labeled Anti-DNA-Frozen. FREEZE IMMEDIATELY. Ship frozen to Covance on day of collection. Refer to laboratory manual for shipping instructions.

Hematology & Glycosylated HbA<sub>1c</sub>: 5 ml lavender top tube. Mix immediately by inverting tube 10 to 15 times. Place in plastic sleeve and seal by tying a knot.

Hematology slides: 2 Slides. Smears made with blood from the collection needle. Place in blue slide mailer.

Urinalysis: 15 ml urine tube with preservative table. Transfer specimen from standard urine collection cup into tube. Do not fill above 13 ml mark. Screw cap on tightly. Place in plastic sleeve and seal by tying a knot. Refrigerated until shipment to Covance.

Creatinine Clearance/Total Protein/24 hour urine: 15 ml blue top tube without preservative. Transfer specimen from the measured urine collection container into the tube labeled 24 HR URINE. Do not fill above 13 ml mark. Screw cap on tightly. Place in plastic sleeve and seal by tying a knot.

Antiphospholipid antibodies: Refer to Covance Manual for instructions.

Serum Beta hCG, Qualitative (optional): Refer to Covance Manual for instructions.

## APPENDIX 15.7 Procedures for DEXA Scanning

At selected centers, patients will undergo dual energy x-ray absorptiometry (DEXA) scans to assess bone mineral density of the lumbar vertebrae and proximal femur. The first measurement must be obtained prior to or within 3 days of the onset of study drug treatment. The second measurement will be obtained at study Completion or within 5 days of Early Termination for those patients completing at least 6 months of treatment.

Copies of the actual DEXA printouts and bone density reports and digital scan data on floppy disks will be provided to Genelabs for file purposes only. Results of the bone density measurements will be recorded by site personnel on the appropriate form.

The site will also provide to Genelabs copies of instrumentation quality control, including values for measurements of anthropomorphic spine phantom. At a minimum, the spine anthropomorphic phantom will be measured on each day that the patient undergoes BMD measurements.

Bone mineral density of proximal nondominant femur (femoral neck, trochanter, and Ward's triangle) and lumbar vertebrae L1-L4 or L2-L4 will be obtained. The scans performed at study completion will be matched to the scan performed at baseline to ensure measurement of identical bone regions.

The same DEXA instrument and, if possible, software, should be utilized for both scans. Additionally, if possible, the same technologist will be utilized at each investigative site for all densitometry scans. For proper evaluation of the bone status, fractured or crushed vertebrae will be excluded from the analysis region.

BMD at proximal femur (femoral neck, trochanter, and Ward's triangle) and average of lumbar vertebrae L1-L4 or L2-L4 will be analyzed using the following statistics: (1) mean at baseline and post-treatment, and % change from baseline for each treatment group will be summarized.

**APPENDIX 15.8 GL 95-02 Schedule of Events (REVISED February 5, 1999)**

Genelabs: DHEA-S Serum Sample to be obtained at the Screening Visit (or Qualifying visit if not obtained at the Screening Visit), and Visits 1 and Medication Completion/Early Termination.

Appendix 15.8  
Schedule of Events

Amended February 5, 199  
Incorporates Amendments 1 and 2

GL95-02  
Study GL95-02

ACTIVITY (CRF)	Screen	Qualifying	V1 13	V2 26	V3 39	Completion/ Early term 52* (*)	Follow Up 68**	Post-Completion Visit (Only for patients who have Already completed GL95-02 Within the last 6 months of the amendment)
Patient Consent & Informat	X							
Inclusion/Exclusion (IEC)		X						
Demography History	X							
Medication History	X							
SLE History	X							
Non-SLE Medication History	X		X			X		
Vitals and Physical Exam	X					X		X
Transvaginal US/Endom: Biopsy (*)						X (*)		
Mammography (*)						X (*)		X
Informed Consent			X			X		
Adverse Events		X	X			X		
Concomitant Medication		X	X			X		X
EKG	X					X****		
DEXA***		X				X		
SLAM Determination	X		X			X		
SLICC Damage Index	X		X			X		
Physician's Global Assessment (VAS)	X		X			X		
SLEDAI Determination	X		X			X		
SF-36*****	X		X			X		
Krupp Fatigue Severity Score*****	X		X			X		
Patient Self Assessment (VAS)*****	X		X			X		
Central: Laboratory Tests	X*****		X			X*****		X
Local: ESR	X		X			X		
Genelabs: DHEA-S Serum Sample	X		X			X		
Pregnancy Test	X	X	X			X		
Comments (as needed)	X	X	X			X	X	
Medication Dispensed		X	X			X		
Drug Accountability Form		X	X			X		
Termination Form								

\*This may also be the baseline visit for patients who elect to enroll into the open label study (GL-95-01).  
 \*\*All patients who elect not to enroll into GL 95-01 are to have a follow-up assessment 6 weeks following their completion or early termination visit from this study.  
 \*\*\*Selected sites only.  
 \*\*\*\*For patients treated 0-6 months  
 \*\*\*\*\*Completed by patient  
 \*\*\*\*\* Following an 8 hour fast, nothing to eat or drink until after all blood and urine specimens have been obtained unless contraindicated (e.g., diabetes mellitus).  
 (\*)= Complete this visit for Early Termination or Completion of the protocol  
 (\*\*) = Only for per- and post-menopausal women with an intact uterus (women who had no hysterectomy)  
 (\*\*\*) = Only for post-menopausal women  
 (\*\*\*\*) = If not performed within the last 12 months

## APPENDIX 15.9 Transvaginal Ultrasound and Endometrial Biopsies

### General:

All post-menopausal women who have not had a hysterectomy are eligible and requested to participate (Please refer to Section 1.6: Estrogen Administration and Endometrial Hyperplasia).

For clinical purposes, the first procedure to be completed will be called "baseline," which may occur after the patient has commenced participation in the study.

### Timing:

1. A transvaginal ultrasound will be obtained from all eligible patients (post-menopausal women with intact uterus) at the Completion Visit. Patients who have completed the study within six months of this amendment should be contacted as soon as possible and be schedule for this procedure.
2. In case of a *normal* Completion Visit – transvaginal ultrasound, a follow-up is not required. No follow-up is scheduled for *normal* Post-Completion ultrasounds.
3. In case of an *abnormal* Post-Completion transvaginal ultrasound (endometrial thickness  $\geq 5$  mm), an *endometrial biopsy* is recommended (unless medically contraindicated). If the endometrial biopsy shows evidence of *endometrial hyperplasia*, the patient will be treated with oral medroxyprogesterone acetate for 3 months. In case of treatment, a follow-up transvaginal ultrasound is suggested after 3 months.

### Procedure (Transvaginal Ultrasound):

Transvaginal Ultrasound measurements will be performed, when possible, at each center by one designated ultrasonographer.

For patients receiving hormone replacement therapy (HRT), ultrasound will not be restricted to a particular time of the medication cycle, but the day of the cycle and type of hormone replacement therapy will need to be recorded. The patient will be requested to withhold HRT medications on the day of the visit until *after* blood samples for hormone measurements have been collected on the day of the procedure.

### Procedure (Endometrial Biopsy):