GL701 (DHEA, prasterone) for the Treatment of Systemic Lupus Erythematosus (SLE) in Women

Briefing Document
FDA Arthritis Advisory Committee

April 19, 2001

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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2 EXECUTIVE SUMMARY

2.1 BACKGROUND

Systemic lupus erythematosus (SLE) is a serious chronic, autoimmune, inflammatory disease that may affect the skin and joints, as well as internal organs and serous membranes. 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.

Current therapies for active SLE are limited and include only hydroxychloroquine, corticosteroids, and immunosuppressive/cytotoxic drugs. Patients are exposed to multiple toxicities, many serious, during treatment with these drugs. Since patients are often dependent on steroids and immunosuppressive drugs, discontinuing them or reducing their dose may cause serious flares while continued use leads to multiple cumulative toxicities.

Although the etiology of lupus is unknown, hormonal influences seem to play a key role in disease development and progression. Dehydroepiandrosterone (DHEA) and its sulfated metabolite, DHEA-S, are the most abundant circulating steroid hormones in humans and are the principal androgens secreted by the adrenal gland. Circulating levels of DHEA and DHEA-S are reduced by approximately 50% in female SLE patients with active disease.

Two clinical studies conducted at Stanford University – one open-label and one double-blind, placebo-controlled - initially suggested that orally administered DHEA may improve manifestations of disease in mild to moderate SLE, reduce steroid requirements, reduce flares, and improve patient's overall self-assessment of the status of her SLE.

The New Drug Application for GL701 (Genelabs' formulation of prasterone [dehydroepiandrosterone, DHEA]) is based primarily on two double-blind placebo-controlled studies in women with SLE: Study GL94-01, which assessed the ability of GL701 to enable steroid reduction to 7.5 mg/day in steroid-dependent patients; and Study GL95-02, which assessed the effects of GL701 on overall signs and symptoms of SLE in patients with active disease. Long term safety data are provided from Study GL95-01, an open-label 1-year extension study. The application is also supported by a double-blind, placebo-controlled, non-US IND study conducted by a licensee in Taiwan (GBL96-01).

The GL701 clinical program has focused primarily on adult women with SLE inasmuch as approximately 90% of affected patients with this disease are women in their childbearing years.

2.2 EFFICACY

In Study GL94-01, women with mild to moderate SLE were randomized to receive GL701 100 mg/day, GL701 200 mg/day or placebo for 7 to 9 months to determine whether GL701 would allow reduction of prednisone to $\leq$ 7.5 mg/day for 2 consecutive months including the last visit while improving or maintaining disease activity (responders). Study patients had been treated with prednisone 10 - 30 mg/day and either a) in the last 12 months attempted to taper prednisone dose but failed and had a stable prednisone dose for at least 6 weeks preceding the study, or b) in whom there had been no attempt to taper in the last 12 months and had been on a stable prednisone dose for at least 3 months preceding the study.

Patients returned at monthly visits, at which time corticosteroid dose was reduced by algorithm: prednisone dose (or its equivalent in other corticosteroids) was reduced if disease activity was stable or improved as assessed by the SLE Disease Activity Index (SLEDAI), a composite score which measures overall disease activity in multiple organ systems.

GL94-01 was the first study of its type to investigate steroid sparing as an endpoint in a therapeutic trial for SLE. Given that there was no precedent for design of steroid sparing studies in SLE, investigator experts could not determine during the planning of this study whether patients with low SLEDAI scores (indicative of low disease activity) should be enrolled, since a low SLEDAI score could either reflect suppression of disease activity by exogenous corticosteroid treatment or relatively inactive disease. If the latter were true, patients might be unnecessarily treated with doses of corticosteroids higher than necessary for maintenance of disease suppression.

Because this issue was impossible to resolve without any prior SLE investigation precedent, an assessment of overall responders by baseline SLEDAI score was conducted while the study was blinded to treatment assignments and showed that patients with low SLEDAI scores (e.g., SLEDAI $\leq$ 2) had much higher responder rates than patients who entered with higher SLEDAI scores. As a consequence, FDA agreed to defining a subgroup of patients with baseline SLEDAI >2 as part of the efficacy analyses.

The study population consisted of 191 patients. The percent of patients who achieved sustained reduction to 7.5 mg/d for at least the last 2 months of the study ("responders") were as follows: for analysis of all randomized patients (N=191) 40.6% for placebo, 44.4% for GL701 100 mg, and 54.7% for GL701 200 mg, (P=0.110, GL701 200 mg vs. placebo). For the patient group with baseline SLEDAI >2 (N=137), responders were 28.9% for placebo, 38.3% for GL701 100 mg, and 51.1% for GL701 200 mg (P=0.031,

GL701 200 mg vs. placebo). In this group, there was a dose response relationship (P=0.033 for linear trend).

Additionally, a treatment effect was evident for the total number of days over the entire 7 month period during which daily prednisone dose was $\leq$ 7.5 mg/day with mean (median) days for all patients showing placebo 71.7 (66.5) vs. GL701 200 mg 92.1 (111.5 days), P <0.069; and for patients with baseline SLEDAI >2, placebo 59.7 (28.0) days vs. GL701 200 mg 93.4 (111.0) days, P <0.013 GL701 200 mg vs. placebo.

In summary, in GL94-01 more GL701 patients than placebo patients were responders: i.e., achieved sustained prednisone reduction without worsening of signs and symptoms of SLE. This difference approached significance in the intent-to-treat patients and achieved significance in those with baseline SLEDAI > 2. There was a dose-response relationship, with the numbers of responders in the GL701 group being intermediate between GL701 200 mg and placebo. The difference in responders appeared early in the study and was maintained for the duration of the study. The mean number of days with a daily dose of prednisone $\leq$ 7.5 mg was significantly greater in the GL701 200 mg group.

In the second study, Study GL95-02, women with mild to moderate active SLE were randomized to placebo or GL701 200 mg/day for 12 months. The primary efficacy objective of the study was to demonstrate improvement or stabilization in the disease and/or its symptoms in women with active SLE. The study population was mild to moderate SLE, defined as patients receiving either no prednisone or up to 10 mg/day (or its equivalent of other corticosteroids). Active disease was initially defined by a criterion of a Systemic Lupus Activity Measure (SLAM) score of $\geq$ 7, but following the findings from the earlier GL94-01 study, the protocol was amended while ongoing and blinded to also require baseline SLEDAI > 2.

Concomitant medications, including NSAIDs, glucocorticoids, anti-malarials, and immunosuppressives were required to be stable for at least 6 weeks prior to enrollment and were to be held stable throughout the duration of the study.

The primary efficacy variable or endpoint was “response.” The response was a per-patient endpoint that integrated the three domains of SLE including disease activity, as measured by the SLEDAI and SLAM; quality of life or constitutional symptoms, as measured by the Patient Visual Analog Scale (VAS) and Krupp Fatigue Severity Score (KFSS); and organ damage, as assessed by clinical deterioration. A responder had to demonstrate improvement or stabilization of each of the above four scoring instruments, and also not experience “clinical deterioration.”

Because there was no precedent for this composite responder definition, which had not been previously validated in a clinical trial, it became clear that it would be difficult to quantify "stabilization" of disease. As a consequence, allowance for minor variability in the scoring instruments was identified and proposed for the definition of responders. Therefore, prior to unblinding the study, a "tolerance window" was defined to ensure that minor variability in these instruments would not confound the primary efficacy analysis for determining improvement and/or stabilization.

An additional efficacy variable defined toward the end of Study GL95-02 was "definite flare" which was defined to be consistent with flare descriptors for the ongoing NIH sponsored SELENA (The Safety of Estrogen in Lupus Erythematosus National Assessment) study in women with lupus, which commenced after the start date of this ongoing study.

Bone mineral density at baseline and at 12 months was measured at 8 study sites on selected patients who had been on corticosteroids for at least 6 months prior to study entry.

Three hundred and eighty-one (381) patients were randomized to Study GL95-02, of whom 346 were in the per-protocol population, which was defined in the statistical analysis plan and which consisted of patients who had been treated for at least 60 days and had at least 1 post baseline assessment. Of these, 265 patients also had baseline SLEDAI >2. Of the 35 patients not meeting the criteria for the per-protocol population, 32 had no post-baseline assessments. The other 3 were excluded because of a major protocol violation (one patient) or receiving less than 60 days study drug (2 patients).

Study GL95-02 confirmed the findings of the earlier study, GL94-01, in that patients with no or minimal SLE activity (defined as SLEDAI $\leq$ 2) should be viewed separately from those with baseline SLEDAI > 2 since a significant ($P < 0.001$) treatment interaction with baseline SLEDAI > 2 (yes/no) was noted.

Among the per-protocol population (N = 346), the percent of patients who were responders were 45.5% of 176 placebo patients vs. 58.2% 170 GL701 200 mg patients, P=0.018; in those with baseline SLEDAI >2, the percent of patients who were responders were 48.0% of placebo vs. 65.9% of GL701 200 mg, P=0.005. In the intent-to-treat population (N = 381), there were also more responders in the GL701 group compared to the placebo group, 51.3% of 189 GL701 patients were responders compared to 42.2% of 192 placebo patients (p=0.074); in those with baseline SLEDAI > 2 group, 58.5% of 147 GL701 patients were responders compared to 44.5% of 146 placebo patients (P=0.017)

Both treatment groups showed improvement in individual scoring instruments, but the mean improvement for the GL701 group was greater than the placebo group for each instrument. In particular, for patients

with baseline SLEDAI >2, the improvement in Patient VAS was greater in the GL701 group (P=0.057 GL701 vs. placebo).

Fewer patients in the GL701 group with baseline SLEDAI >2 experienced a definite flare: 31 (23.5%) of 132 GL701 patients had at least one definite flare compared to versus 41 (30.8%) of 133 placebo patients, a trend favoring GL701, but the difference was not statistically significant (P=0.201).

At eight investigator sites, thirty-seven of the patients who had been receiving chronic corticosteroids ($\geq$ 6 months) prior to enrollment underwent bone mineral density measurements by DEXA scanning at baseline and at 12 months. In these patients receiving chronic corticosteroid treatment, there was a significant decrease in bone density in the placebo group. By contrast, bone density increased in the GL701 group. The differences at 12 months between GL701 and placebo were seen most prominently in the spine, where the mean decrease of 1.78% in bone density in the placebo group is compared to a mean increase of 1.83% in the GL701 group (P=0.004).

With respect to the objective of the GL95-02 study, the GL701 group had approximately a 35% increase in the proportion of responders, and a 24% decrease in proportion of patients with definite flares .

Supportive data for efficacy are provided from a non-US IND study conducted in Taiwan by a licensee. This study was similar in design except that it was a 6-month study. Ninety-seven percent (97%) of the patients entered with baseline SLEDAI >2; also, 97% of the patients were receiving corticosteroids at study entry. The primary endpoint was percent improvement in SLAM.

The GL701 group demonstrated a greater reduction from baseline for SLAM score in both mean and median scores as compared to the placebo group, but the difference was not significant. The difference in mean change in patient VAS was statistically significant. The GL701 group improved, while the placebo group worsened (P=0.005). Utilizing the same flare definition as in Study GL95-02, the GL701 group in the Taiwan study had fewer patients with at least one definite flare. The number of patients with definite flares in the GL701 group was decreased 46.0% compared to placebo (18.3% vs. 33.9%, p = 0.044 based on time to first flare).

Thus, the overall results of the primary and secondary efficacy analyses for the Taiwan study consistently showed benefit for GL701 in the treatment of SLE.

In summary, consistent efficacy findings have been observed across all studies and have demonstrated improvement in all three domains of SLE in GL701-treated patients. Reduction in manifestations of SLE or improvement in the area of SLE disease activity was demonstrated by the increase in proportion of

responders and decrease in proportion of patients with flares. Achievement of sustained reduction of corticosteroids in corticosteroid-dependent patients, without worsening of disease, as well as improvement in bone mineral density in patients receiving corticosteroids chronically, are important benefits for the domain of SLE damage. Finally, a benefit in the patients' overall assessment of quality of life or constitutional symptoms was demonstrated by improvement in the Patient VAS, a finding which was consistently observed in these studies.

2.3 SAFETY

In the double-blind, placebo-controlled trials and the open-label extension study which followed completion of the double-blind studies, 387 women have received GL701 for at least 6 months; 242 for $\geq$ 12 months, and 138 for $\geq$ 18 months, and 36 for >24 months. The principal adverse events and biochemical changes associated with treatment with GL701 were principally related to its androgenic properties. No new unexpected safety findings emerged with continued treatment with GL701 for up to 2 years.

Adverse events that were each statistically significantly more common in GL701 200 mg-treated patients compared to placebo were acne (36.0% vs. 15.2%) and hirsutism (14.2% vs. 2.3%), as well as hypertension (7.9% vs. 2.7%) , hematuria (3.6% vs. 0.4%), and increased creatinine (2.4% vs. 0%). Acne and hirsutism were expected androgenic events; and the difference between placebo and GL701 was clinically meaningful as well as statistically significant. Hematuria, hypertension and creatinine increase occurred in only small numbers of patients. Their relationship to GL701 and their clinical significance wass less clear. These events were viewed in greater detail and are discussed in **Section 7.4**.

For hypertension, no differences between treatment groups were observed in a composite measure which integrated the number of patients experiencing new onset hypertension, or experiencing an increase in hypertension, or requiring an additional anti-hypertensive medication or an increase in dose of existing anti-hypertensive medications.

For the adverse events of "hematuria" or "creatinine increase," there was no consistent association with renal dysfunction.

Serious adverse events occurred in 38 GL701 200 mg, 7 GL701 100 mg, and 39 placebo patients. Only 3 of these events were assessed by the investigators as related to study drug: 2 in placebo and 1 in GL701.

For clinical laboratory assessments, there were no meaningful or significant differences between treatment groups in hematology or liver function parameters. BUN and creatinine levels did not change

during study and were similar within or between treatment groups. Mean changes in 24-hour urine protein excretion increased in all treatment groups, but to a greater extent in GL701 patients. However, a few patients with very high values impacted 24-hour urine protein; and median changes were only slightly higher in the GL701 groups.

Decrease in serum complement changes, particularly C3, were more common among patients treated with GL701. Most patients remained within the normal range; 16% of patients on GL701 200 mg went from normal to low C3 (< 85 mg/dl), compared to 6% of placebo patients at last visit. Few of the patients who reduced complement exhibited other manifestations of renal lupus including worsening of proteinuria, new hematuria, or addition of new immunosuppressives; those that did occur were equally distributed between the GL701 and placebo-treated groups. An androgenic effect on hepatic complement synthesis is postulated as the cause for the reduced C3 complement rather than an effect on inflammation-related consumption.

Changes in serum lipids were consistent with changes associated with androgenic steroids. Total cholesterol, HDL-C, and triglycerides were decreased in GL701-treated patients in comparison to placebo patients (**Figure 2-1**). These changes were seen by three months with relatively little further progressive decrease. The mechanism of this androgenic-induced decrease in serum lipids is believed to be enhanced hepatic clearance of HDL-C and triglycerides.

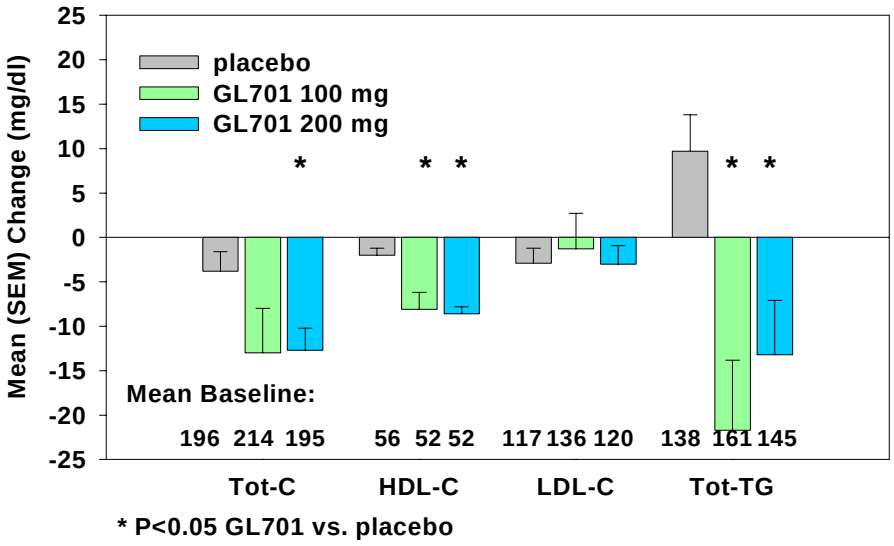


Figure 2–1: Lipid Changes

The hormonal effects of GL701 were primarily androgenic in nature with significant increases in total testosterone, but primarily to levels at the upper range of normal for women. Serum estradiol did not

change in pre-menopausal women, while in post-menopausal women, increases in serum estradiol were primarily to levels consistent with hormone replacement therapy. Only a few post-menopausal SLE patients achieved levels in the pre-menopausal range.

There were few reports of menstrual bleeding abnormalities either in pre- or post-menopausal patients suggesting there were no significant estrogenic effects on the endometrium. Additionally, mammography and uterine ultrasound measurements on some of the post-menopausal patients who had participated in these studies did not show evidence of neoplasia of the breast or hyperplasia or neoplasia of the endometrium.

There were 3 (1.5%) cases of breast cancer in 206 GL701-treated patients older than 45 years and 1 (4.2%) case in 24 placebo patients (never received GL701) of the same age group. Expressed as a rate per-patient year of observation for patients 45 years or older, these rates are 4.6/1000 for GL701 and 6.5/1000 for placebo. These are similar to breast cancer rates recently reported in the medical literature for post-menopausal women.

Taking this data as a whole, it would appear that increased risk, if any, of breast cancer associated with GL701 therapy should be low. GL701 therapy produces estradiol levels lower or similar to those with HRT and GL701 therapy is not accompanied by progestin therapy. The data from the GL701 clinical trials so far do not suggest an increased rate of breast cancer.

2.4 CONCLUSIONS

Four different studies, all in women with SLE, support the proposed indications for GL701:

1) Improvement in disease activity and/or its symptoms in women with mild to moderate systemic lupus erythematosus,

2) Reduction of corticosteroid requirements in women with mild to moderate systemic lupus erythematosus.

Improvement in GL701-treated patients has been consistently shown in Phase II studies conducted at Stanford University and subsequent studies conducted by the Sponsor and in Taiwan. Improvement has been demonstrated in all three domains of SLE.

3 BACKGROUND

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 (American College of Rheumatology Ad Hoc Committee, 1999).

Although the etiology of lupus is unknown, hormonal influences seem to play a key role in disease development and progression. Beyond the increased incidence in women, several studies have noted that alterations in estrogen and androgen metabolism occur in patients with lupus. Decreased levels of androgens (androstenedione, dehydroepiandrosterone [DHEA], DHEA-S, and testosterone) have been observed in female lupus patients, especially in those with active disease (Lahita, 1987; Jungers, 1983).

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.

Most lupus patients do not respond to conservative therapy and require glucocorticoids for control of disease activity. In the Johns Hopkins Lupus Cohort, comprising of 539 patients, 89% had used prednisone, 21% of whom had been treated on one or more occasions with doses over 60 mg/day for at least 2 months. Most patients had used prednisone at doses above 10 mg/day (Zonana-Nacach, 2000).

Despite the fact that they are the mainstay of treatment for most lupus patients, glucocorticoids are well-known to be associated with significant toxicity including ischemic cardiovascular disease, serious infection, hyperglycemia, hypertension, osteoporosis, muscle wasting, avascular necrosis of bone, and cataracts (Zonana-Nacach, 2000). Female SLE patients are at a 5-fold risk of osteoporotic fractures (Ramsey-Goldman, 1999), and a 1.6-fold risk of ischemic necrosis (Zonana-Nacach, 2000). Patients dying early from lupus succumb to complications of lupus and/or infection while those dying after 5 years

of disease often succumb to atherosclerotic complications, which may be related in part to chronic corticosteroid therapy (Urowitz, 1999, 2000).

Flares occur commonly among SLE patients. In the Johns Hopkins Lupus Cohort, the incidence of flare was 0.65 per patient-year of follow-up with the median time from first study visit to a flare being 12 months (Petri, 1991). While most flares involve "minor" organ systems, i.e. constitutional (fatigue) musculoskeletal, and cutaneous, it is of interest that in the Hopkins cohort, prednisone dose was increased in 39.7% of the flares (Petri, 1991). Furthermore, of 261 patients, 56.3% were hospitalized over a 2 year period from 1989 to 1990 (Petri, 1992). Prednisone dose over 10 mg/day was one of the risk factors for infection requiring hospitalization (P=0.04), as was use of immunosuppressive drugs (P=0.003).

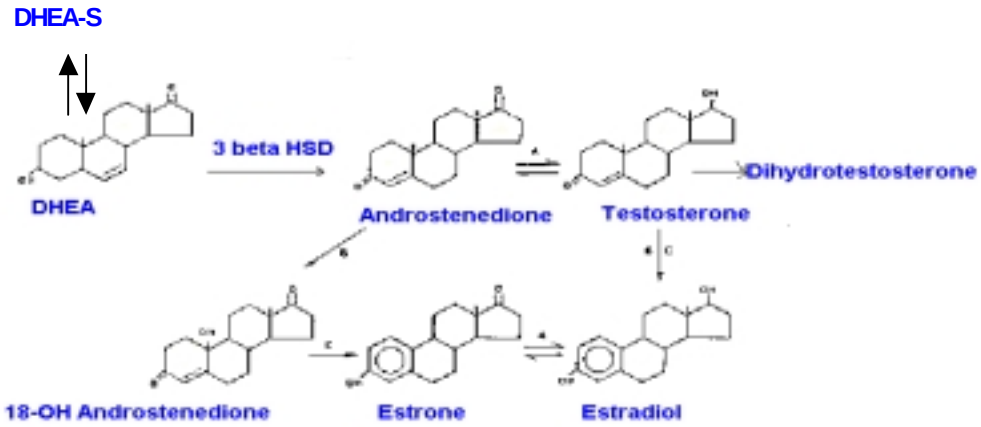
Thus, an extremely important goal in the treatment of SLE is to reduce glucocorticoids to the lowest dose required to maintain suppression of SLE activity. However, during glucocorticoid taper, patients may experience symptoms of steroid withdrawal (e.g., joint pain, malaise) and the underlying disease may flare, thus perpetuating the need for treatment with glucocorticoids to control flare in this disease.

More aggressive management is often warranted in the treatment of lupus. In the Johns Hopkins lupus cohort alone, 34% of patients were using cytotoxic drugs (Zonana-Nacach, 2000). 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, hepatitis, pancreatitis, nausea and vomiting, and infections. Cyclophosphamide can result in urinary bladder toxicity, sterility, teratogenic effects, infections, and cancer.

Progression of SLE is highly variable and is difficult to predict from one individual to another. Lupus remains a serious disease with a 10-year mortality rate of approximately 10 to 20% (Uramoto, 1999).

3.1 RATIONALE FOR DHEA AS A THERAPY IN SLE

DHEA is a naturally occurring steroid produced by the adrenal glands, testes, ovaries and brain. Its metabolite, DHEA sulfate (DHEA-S), is the most abundant circulating adrenal steroid in the human body and is converted by peripheral tissues containing DHEA sulfatases, including lymphocytes and macrophages, to DHEA. DHEA is in turn metabolized to androstenedione as well as other potent androgens: testosterone, dihydrotestosterone and estrogens, including estrone and estradiol. As a biologically inactive precursor, selective conversion of DHEA to other androgenic and estrogenic steroids enables metabolism on a tissue-specific basis, a concept known as "intracrinology" (Labrie, 1995).



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

Figure 3–1: Downstream Metabolites of DHEA

As described above, endogenous levels of androgens (androstenedione, DHEA, DHEA-S and testosterone) are decreased (approximately 50%) in women with SLE, especially in those with active disease (Lahita, 1987; Jungers, 1983).

The abnormalities contributing to low DHEA-S concentrations in this disease are poorly understood, but may be related to defects in the hypothalamic pituitary adrenal axis or direct suppression of adrenal androgen secretion by inflammatory cytokines including IL-1 and IL-6, the latter of which is significantly elevated in active SLE (Brink, 1999; Straub, 2000). DHEA has been shown in vitro to directly suppress release of IL-6, IL-1 and TNF-α from human mononuclear cells (Straub, 1998; Padgett, 1998) as well as IL-6 from bone marrow stromal cells (Gordon, 2000); whether these effects occur *in vivo* during treatment with DHEA, however, has not been determined.

Circulating levels of endogenous DHEA and DHEA-S, already low in active SLE disease, are further reduced during administration of glucocorticoids (Hedman, 1989).

In animal models of SLE, administration of androgens, including DHEA, resulted in delayed formation of anti double-stranded DNA antibodies (Siiteri, 1980; Roubinian, 1977; Roubinian, 1979a) and increased survival in hybrid NZB/NZW mice (Melez, 1980; Roubinian, 1979b, Lucas, 1985). Additionally, DHEA may be an important regulator of the immune system by up-regulating IL-2 secretion by activated T cells as demonstrated in both murine and human in vitro assays (Daynes, 1990a; Suzuki, 1991).

Two clinical studies conducted at Stanford University - one open-label and one double-blind, placebo-controlled—initially suggested that orally administered DHEA may improve manifestations of disease in mild to moderate SLE (van Vollenhoven, 1994, 1995). In the placebo-controlled study, concomitant doses of glucocorticoids were decreased, while disease activity as assessed by SLE Disease Activity Index (SLEDAI) score and patient and physician assessment (Visual Analog Scale [VAS]) stabilized or improved. Patient assessment of disease activity improved significantly in the DHEA group compared with placebo, and the number of disease flares (determined clinically by the investigator) experienced by the DHEA treatment group was significantly less than in the placebo treatment group (van Vollenhoven, 1995).

Based on the pre-clinical and clinical observations noted earlier, including the pilot studies at Stanford University, the development of GL701 (Genelabs' formulation of prasterone [dehydroepiandrosterone, DHEA]) in SLE was initiated. GL701 is a pharmaceutical preparation of prasterone, and should be distinguished from DHEA currently marketed as dietary supplements, which are unregulated as to purity or potency, and may vary substantially in content (as much as 0 to 150% of labeled amount) (Parasampuria, 1998).

4 DEVELOPMENT OF GL701 FOR SYSTEMIC LUPUS ERYTHEMATOSUS

4.1 CLINICAL STUDIES SUPPORTING EFFICACY AND SAFETY OF GL701 IN SLE

Four different studies, all in women with SLE, support the proposed indications:

1. Improvement in disease activity and/or its symptoms in women with mild to moderate systemic lupus erythematosus
2. Reduction of corticosteroid requirements in women with mild to moderate systemic lupus erythematosus

These studies are summarized below by number and in **Table 4-1**.

GL94-01, a randomized, parallel group double-blind placebo-controlled study comparing placebo to 100 mg/day and 200 mg/day of GL701, where the primary efficacy variable was “steroid sparing”, or reduction in corticosteroids in corticosteroid dependent patients, without worsening of disease activity.

GL95-02, a randomized, parallel group double-blind placebo-controlled study comparing placebo to 200 mg/day of GL701 in patients with active SLE, where the primary efficacy variable was improvement or stabilization of disease activity while maintaining a constant dose of corticosteroids and other SLE medications.

GBL96-01, (a foreign (Taiwan) study conducted by a licensee, not under US IND), a randomized, parallel group double-blind design, placebo-controlled study comparing placebo to 200 mg/day GL701, where the objective was improvement in SLE disease activity while maintaining a constant dose of corticosteroids and other SLE medications.

GL95-01, an open-label extension study in which patients who completed therapy in either one of the double-blind trials (GL95-02 or GL94-01) received open-label GL701. This study provides long term safety information for GL701.

Additional supportive efficacy data come from publications of the studies conducted by Stanford University in which DHEA was studied under an investigator IND (#37,873) (van Vollenhoven, 1994, 1995).

Also study **GL97-01**, a randomized, parallel group, double-blind, placebo-controlled study in men with SLE is also ongoing, with 28 patients enrolled. The study remains blinded and as of the date of this submission, only serious adverse event data (blinded to treatment group) are available.

Table 4–1: GL701 Clinical Studies

Study No.	Patient Population	Objective	Total Patients	Duration of Treatment	Duration of Study	Design
Well Controlled Studies						
GL94-01	Women with active SLE	Reduction in corticosteroids in corticosteroid dependent patients, without worsening of disease activity	191	7-9 mos.	6/94 – 6/96	Prospective, Randomized Double-blind, Placebo-controlled
GL95-02	Women with active SLE	Improvement or stabilization of SLE	381	12 mos.	2/96 – 6/99	Prospective, Randomized Double-blind, Placebo-controlled
GL97-01	Men with active SLE	Improvement in SLE	28	12 mos. + 12 mos. Open label	1/98 - On-going	Prospective, Randomized Double-blind, Placebo-controlled
Well Controlled Studies, Foreign Source						
GBL96-01 (Non-US IND)	Women with active SLE in Taiwan	Improvement of SLE	120	6 mos.	2/97 – 7/99	Prospective, Randomized Double-blind, Placebo-controlled
Uncontrolled Studies						
GL95-01	Patients who completed either GL94-01 or GL95-02	Long term safety evaluation in open-label extension study for patients completing either of the US double-blind studies	371	12 mos.	3/95 – 9/00	Open-label Extension
Studies Reported in the Medical Literature						
van Vollenhoven, 1995	Women with SLE	Improvement in SLE	28	3 mos.	Not Reported	Prospective, Randomized Double-blind, Placebo-controlled
van Vollenhoven, 1999	Patients with severe SLE (men and women)	Improvement in SLE	19	6 mos.	Not Reported	Prospective, Randomized Double-blind, Placebo-controlled
van Vollenhoven, 1998	Women with SLE	Safety and Efficacy	50	12 mos	Not Reported	Open-label

Study No.	Patient Population	Objective	Total Patients	Duration of Treatment	Duration of Study	Design
Barry, 1998	Women with SLE	Dose response	23	6 mos	Not Reported	Open-label

4.2 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM FOR GL701

The GL701 clinical program has focused primarily on adult women with SLE inasmuch as approximately 90% of affected patients with this disease are women in their childbearing years (American College of Rheumatology Ad Hoc Committee, 1999). Additionally, the hormonal rationale (low levels of endogenous DHEA in women with lupus) for using DHEA and other androgens in women with lupus is not as well established for the male or pediatric lupus population.

Designing a clinical development plan in SLE was particularly difficult because SLE is preeminently a multi-system disease and because no drugs have been approved for SLE in over 40 years. In particular, although there had been treatment trials for organ-specific manifestations, with the possible exception of a smaller withdrawal study of hydroxychloroquine in SLE (Canadian Hydroxychloroquine Study Group, 1991) there had been no experience with large, well-controlled treatment trials which examined overall efficacy for lupus. As a result, there were no pre-existing models for clinical trial design, key enrollment criteria, and, especially important, no established efficacy endpoints.

Because of the multi-system nature of SLE, it is difficult to specify a single primary efficacy endpoint, further compounding the difficulty in designing clinical trials in SLE. Additionally, although there are a number of SLE scoring instruments, such as the SLEDAI or Systemic Lupus Activity Measure (SLAM), none has been validated for assessing change in disease activity in a controlled clinical trial.

Such issues relating to the design of controlled clinical studies in SLE were discussed with the US Food and Drug Administration (FDA) and consultants prior to initiating the clinical studies of GL701. Reduction in corticosteroid dose was seen as a desirable outcome of treatment that could serve as an efficacy endpoint. It was agreed that one study, a Phase II/III efficacy study, would use steroid sparing as an endpoint.

While the Phase II/III steroid sparing study was ongoing, plans for a second Phase III study were initiated. The intended purpose of the second study was to evaluate improvement in disease manifestations as an efficacy endpoint, rather than steroid sparing. However, prior to the finalization of its protocol and due to the lack of previous clinical trial experience in the area of SLE, the FDA suggested

that the GL701 clinical development plan be subjected to an Advisory Committee review. In March 1995, a closed session meeting of the Arthritis Advisory Committee (AAC) was held to discuss some fundamental issues surrounding the GL701 clinical development program, including the design of a second Phase III clinical study. In that meeting, a "per-patient" endpoint was identified as generally favored. Genelabs' plan to use "steroid sparing" as an endpoint in the first pivotal trial and an endpoint of improvement in disease manifestations was deemed adequate to support an NDA.

As expected, experienced gained during the trials had an inevitable impact on the final detailed statistical analysis plan for each study. However, consistent with the principles in the final FDA guidance document "E9 Statistical Prinicples for Clinical Trial" (*ICH guideline Guidance on Statistical Principles for Clinical Trials*), the statistical analysis plans were finalized before the blind was broken and all confirmatory analyses were based on the protocol (including procotol/IND amendments) for each study.

4.3 PHARMACOLOGY

4.3.1 Background

GL701 provides an exogenous source of DHEA, which is the major hormone produced by the adrenal glands. DHEA, a 19-carbon steroid synthesized within the adrenal gland, is secreted primarily as its sulfated ester metabolite, DHEA-S, which is the most abundant circulating steroid in the human, up to a 30-fold concentration greater than cortisol. On a molar basis, endogenous circulating concentrations of DHEA-S are approximately 250 and 500 times higher than those of DHEA in women and men, respectively (Carlstrom, 1988; Labrie, 1997).

The direct biological actions of DHEA and DHEA-S remain unknown as no functional receptor for either is known, but both are metabolized to androgenic and estrogenic steroids in nonadrenal tissues and serve as a mechanism for delivery of androgen and estrogen precursor substrate to target tissues. These target tissues can adjust the formation and metabolism of sex steroids to local requirements to reflect the peripheral conversion of DHEA or DHEA-S into more potent steroids without release into the extracellular space (Labrie, 1995). 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. From puberty on, DHEA-S blood levels in men are significantly higher than those in women (Orentreich, 1984). Unlike cortisol, levels of DHEA-S decline progressively thereafter, to approximately 5 to 10% of peak values at age 60 to 70 (Orentreich, 1984; Carlstrom, 1988; Labrie, 1997). Age, genetic

factors and gender account for a wide variation in circulating levels of DHEA and DHEA-S (Rotter, 1985).

Orally administered DHEA undergoes rapid sulfoconjugation in intestinal cells to DHEA-S (Baulieu, 1965). The average ratio of the serum concentration of DHEA-S to DHEA is approximately 500-800:1.

Both DHEA and DHEA-S are bound to serum albumin, globulins and steroid sex hormone binding globulin (SHBG) (Dunn, 1981). Approximately 88.1% of circulating DHEA is bound to albumin, 7.88% to SHBG, and < 0.1% to cortisol binding globulin, leaving 3.93% unbound in normal women in the follicular phase of the menstrual cycle (Dunn, 1981).

DHEA-S is strongly bound to albumin in blood and undergoes renal tubular reabsorption (Longcope, 1995), both of which contribute to its very slow clearance from blood and its long half-life.

Arlt (1998, 1999) reported in females a mean DHEA $t_{1/2}$ of 8.9 ± 3.6 and 7.6 ± 2.7 hours following oral administration of DHEA 50 or 100 mg, respectively, and a $t_{1/2}$ for DHEA-S of 13.2 ± 2.7 and 12.1 ± 2.8 hours following oral administration of DHEA 50 and 100 mg, respectively.

In a Genelabs' sponsored single-dose pharmacokinetic study (GL97-02), the half-life ($t_{1/2}$) was calculated to be approximately 20 hours for DHEA and DHEA-S. However, these calculations are confounded by variable endogenous (i.e. circadian variability) DHEA and DHEA-S levels. These may be further confounded by possible negative feedback mechanisms for suppression of DHEA release. The more relevant approach to estimating the $t_{1/2}$ of DHEA and DHEA-S can be determined from the other Genelabs' sponsored steady-state pharmakokinetic study (GL99-01). This study showed that steady-state was reached at 2 days, which equates to a half-life of approximately 7-8 hours for both DHEA and DHEA-S (see **Figure 4-1**).

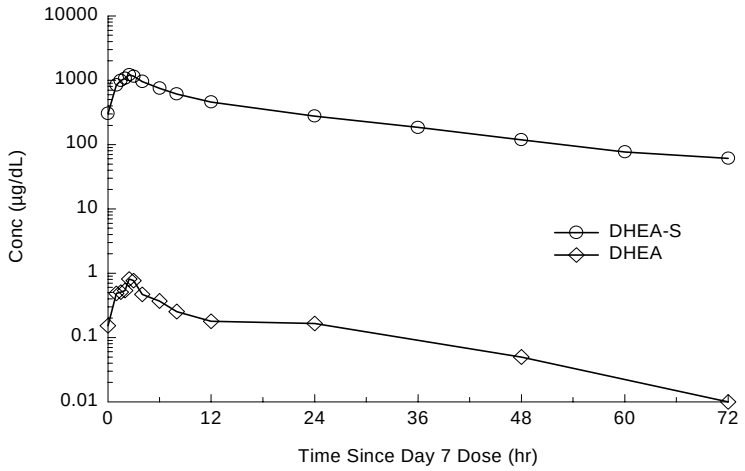


Figure 4-1: Achievement of Steady-State DHEA and DHEA-S (GL99-01)

4.3.2 Pharmacokinetic Studies

One prednisone interaction study after oral administration of GL701 to pre-menopausal women and two bioequivalence studies in pre- and post-menopausal women have been conducted to support the pharmacokinetics of GL701. Brief summaries of the relevant data from the studies are provided below.

4.3.2.1 Prednisone Interaction Study (GL96-02)

The objective of this study was to assess prednisolone, prednisone pharmacokinetics pre- and post-GL701 treatment as well as pharmacokinetics of DHEA and DHEA-S during chronic oral administration of GL701 to 14 healthy pre-menopausal women.

The study was comprised of two inpatient phases. Baseline evaluations were conducted within 4 days of onset of menses and included collection of a 24-hour serum profile of endogenous circulating DHEA and DHEA-S concentrations. On the next day, a single oral dose of prednisone, 20 mg, was administered following which prednisone/prednisolone blood levels were measured over the next 32 hours. Subjects then received GL701 200 mg/day for 30 days.

On Day 29, again within 4 days of onset of menses, administration baseline procedures were repeated, including collection of 24-hour DHEA and DHEA-S profiles following adminstration of GL701 200 mg. On Day 30, subjects received GL701 200 mg coadministered with a single oral dose of prednisone 20 mg and blood samples were collected serially up to 32 hours for assessment of prednisone, prednisolone, and DHEA/ DHEA-S blood levels.

A. Results

Pharmacokinetic parameters of prednisolone from 20 mg prednisone, as assessed by C_{max}, $t_{1/2}$, and AUC were not affected by 200 mg/day of GL701 in multiple doses. Chronic administration of GL701 200 mg/day did not affect the plasma protein binding of prednisolone . After multiple doses of GL701 of 200 mg/day, the ratio of prednisolone to prednisone area-under-the-curve (AUC) was not affected.

Administration of GL701 produced levels of DHEA and DHEA-S significantly greater than endogenous plasma concentration. Mean (SD) maximal concentrations (C_{max}) measured for DHEA and DHEA-S, without correction for endogenous DHEA and DHEA-S, were 1.66 (0.54) and 975 (260) µg/dl , while T_{max} occurred at 3.0 (1.3) and 2.4 (0.9) hours, respectively. Mean area-under-the curve values were 20.84 (6.42) and 11489 (4682) mg•hr/dl.

4.3.2.2 Pharmacokinetic Assessments in Post Menopausal Women (GL99-01)

Pharmacokinetic data was collected as part of two different bioequivalence studies (Studies GL97-02 and GL99-01). GL97-02, was a single dose study with GL701 200 mg and the other study, GL99-01, was a 7-day GL701 200 mg study. Since the 7-day study (GL99-01) collected pharmacokinetic assessments as well as limited pharmacodynamic data using the proposed GL701 commercial formulation, data from only this study is presented.

Study GL99-01 was an open-label, randomized, multiple dose, steady-state, two-treatment cross-over pharmacokinetics/pharmacodynamics study in post-menopausal women. The objective of this study was to demonstrate bioequivalence between a GL701 lot containing a single polymorph form of prasterone (DHEA), which is the proposed commercial forumlation and a lot of GL701 used in a pivotal clinical trial (containing mixed polymorph forms of prasterone). Trough levels of DHEA and DHEA-S were obtained daily for 6 days during treatment, and a full pharmacokinetic profile was obtained on day 7 for each of two GL701 drug lots. A one week washout period was required between treatments.

A. Results

A total of 39 subjects completed the two period cross-over study. The mean multiple dose pharmacokinetic parameters for adjusted (baseline substracted) serum DHEA and DHEA-S concentrations are summarized in **Tables 4-2** and **4-3** for the proposed commercial formulation. One subject was not evaluable because many of her Day 7 serum concentrations were below the Day 1 endogenous concentration.

Table 4–2: Summary of Estimated Mean Pharmacokinetic Parameters for Serum DHEA (N=38) Adjusted for Baseline

Parameters	GL701 Mean (SD)
$AUC_{(144-168)}$ (μg•hr/dl)	8.359 (3.668)
C_{max} (μg/dl)	0.939 (0.655)
T_{max} (hr)	2.5 (0.6)

Table 4–3: Summary of Estimated Mean Pharmacokinetic Parameters for Serum DHEA-S (N=38) Adjusted for Baseline

Parameters	GL701 Mean (SD)
$AUC_{(144-168)}$ (μg•hr/dl)	13995 (4800)
C_{max} (μg/dl)	1295 (358)
T_{max} (hr)	2.4 (0.5)

4.3.3 DHEA-S Levels from GL701 Controlled Clinical Studies

Serum levels of DHEA-S, obtained 24 hours after last dose, were measured in both GL94-01 and GL95-02. As shown in **Figures 4-2** and **4-3** below, pharmacologic levels of DHEA-S were achieved at last visit 10 to 20 times higher than baseline with mean levels for GL701 200 mg of 800 to 900 μg/dl for both studies. These levels are also much higher than the upper range of normal, approximately 260 μg/dl, for DHEA-S in healthy subjects. In Study GL94-01, dose proportionality was shown, with mean levels in the GL701 100 mg group approximately 50% of those in the GL701 200 mg group.

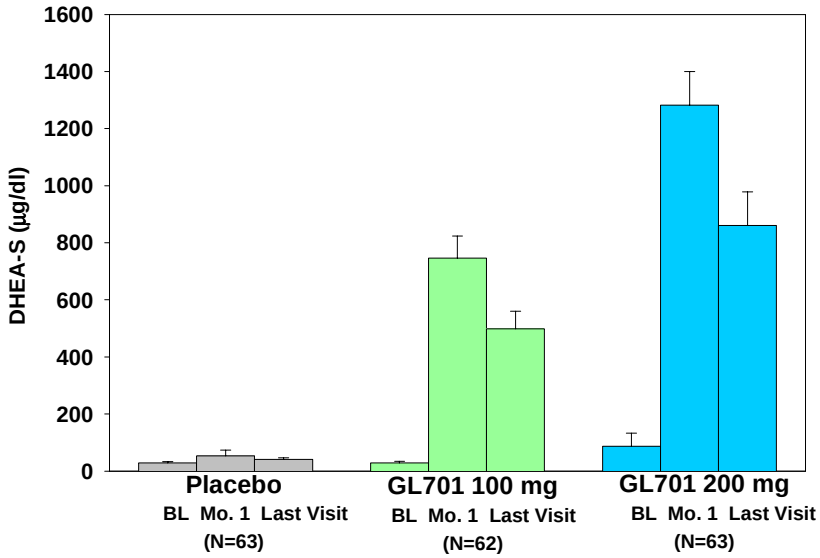


Figure 4-2: Serum DHEA-S Levels at Baseline (BL), Month 1 and Last Visit (GL94-01)

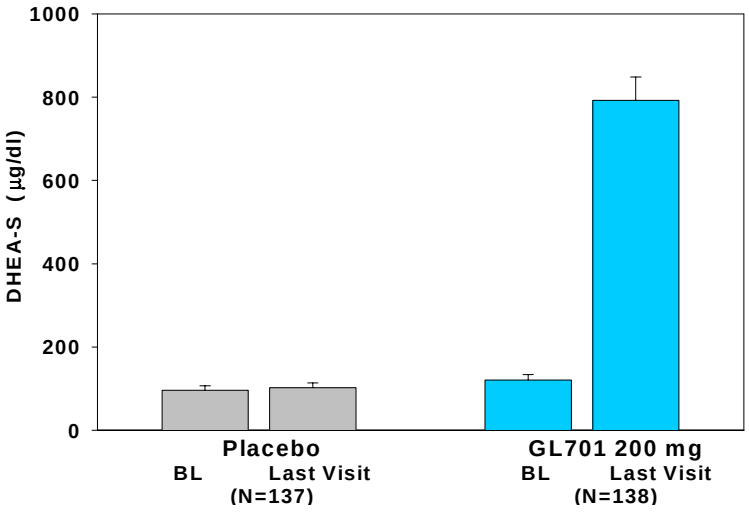


Figure 4-3: Serum DHEA-S Levels at Baseline (BL) and Last Visit (GL95-02)

In Study GL95-02, approximately 55% of patients were receiving corticosteroids (prednisone or other corticosteroids) at study entry. As shown in **Figure 4-4** below, those patients on corticosteroids had much lower endogenous levels of DHEA-S, compared to those not receiving corticosteroids. These lower endogenous DHEA-S levels may represent suppression of DHEA production by corticosteroids, greater severity of disease in patients receiving corticosteroids, or both. This figure also demonstrates that administration of GL701 200 mg achieves DHEA-S levels far above baseline, even in those receiving corticosteroids.

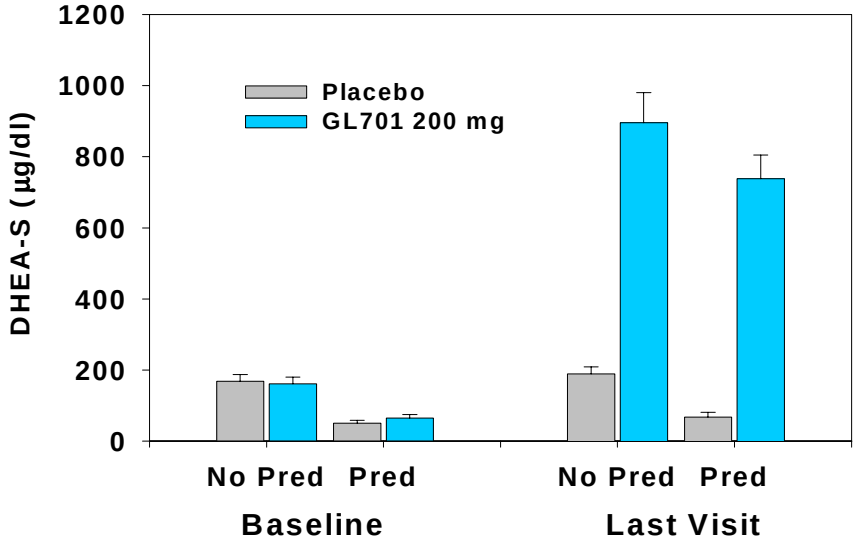


Figure 4-4: DHEA-S Serum Levels by Baseline and Last Visit Prednisone Use

5 ORGANIZATION OF CLINICAL RESULTS

Because the two primary efficacy, placebo-controlled studies, GL94-01 (corticosteroid reduction) and GL95-02 (improvement in SLE) had very different study designs and efficacy endpoints, pooling of efficacy data is not meaningful. Consequently, results pertinent to the efficacy of GL701 in SLE are presented by individual study. Similarly, the supportive efficacy results of the Taiwan Study, GBL96-01, are presented separately.

Pertinent data to the safety of GL701 are pooled from the two primary efficacy, double-blind, placebo-controlled studies. Additional safety data, presented separately, is available from the double-blind placebo-controlled study conducted in Taiwan, GBL96-01. Long term safety of GL701 is assessed by analyzing the data from patients who participated in the double-blind, placebo-controlled studies, GL95-02 and GL94-01, and subsequntly enrolled in the open-label extension study GL95-01. Depending on their treatment assignment in the placebo-controlled studies, such patients either continued to receive GL701 or switched from placebo to GL701 upon enrolling in the open-label extension study.

6 WELL CONTROLLED STUDIES

6.1 STUDY GL94-01 (CORTICOSTEROID REDUCTION STUDY)

Study GL94-01was a Phase II/III study assessing two different doses of GL701. This study compared the proportion of patients achieving sustained reduction of daily corticosteroid dose, without worsening of signs and symptoms of SLE, in the placebo and GL701 groups. Duration of treatment was approximately 7 months.

6.1.1 Protocol Development

Based on pre-IND discussions with FDA and consultants, it was decided that the primary efficacy variable for the corticosteroid reduction study should be, for patients who were corticosteroid dependent, a reduction of the patients' current prednisone dose to 7.5 mg/day (upper limit of physiologic levels) or less, without worsening of SLE.

The design of the steroid sparing study was a forced titration; i.e., the patient's steroid dose at each monthly visit was to be reduced, by algorithm, if her disease activity was stable or improved. However, when a patient worsened or flared, the associated increase in corticosteroid dose, if any, required to treat the patient's exacerbation was at the physician's discretion and not by algorithm. The steroid reduction algorithm was based on the patient's disease activity improving or being stable, which was defined as no change in or a decrease in SLEDAI score in comparison to her previous visit. As such, one of the issues discussed at the pre-study investigator meeting was whether patients with low SLEDAI scores, and especially those with SLEDAI scores of 0, should be enrolled into the study. There was concern that those patients with low SLEDAI scores had inactive disease, and therefore would not be affected by steroid reduction, i.e., might not be steroid dependent. However, some investigators and consultants felt that if patients were truly dependent on steroids, their low SLEDAI scores represented active disease suppressed by corticosteroids, which would worsen or flare as soon as their corticosteroids were reduced. Therefore, because there was no experience with such trials, it was decided not to exclude patients with low SLEDAI scores. The concern regarding enrollment of potentially inactive SLE patients was revisited prior to unblinding of the study.

In addition it was recognized that because of the forced downward titration of steroid dose as the patients' disease improved or remained stable, other evaluations of disease activity such as SLEDAI, etc., would not be expected to improve.

The doses and regimen for this study of 100 or 200 mg GL701 to be taken in the morning as a single dose were selected empirically on the basis of the previous clinical experience from the Stanford University studies. The treatment period was defined as 7 months, unless an additional 1-2 months was required to demonstrate sustained steroid reduction in patients who achieved physiological levels only by month 6 or 7. The 7-month period appeared to be an appropriate amount of time to identify efficacy, especially based upon the evidence of efficacy that was seen at 3 months in the Stanford University studies.

In early 1997, due to previous concerns regarding enrollment of patients with inactive SLE into Study GL94-01, it was recognized that a relatively large number of patients with low SLEDAI scores at baseline, especially SLEDAI = 0, had been enrolled. Therefore, a pooled response rate (while the study was ongoing and blinded) categorized by baseline SLEDAI score was evaluated. It was noted that an unexpectedly high response rate (treatment group combined response rate of approximately 65%) was evident in those patients with the mildest disease (baseline SLEDAI $\leq$ 2), with an inflexion point or sharply decreasing response rate for patients with baseline SLEDAI values > 2 (**Figure 6-1**).

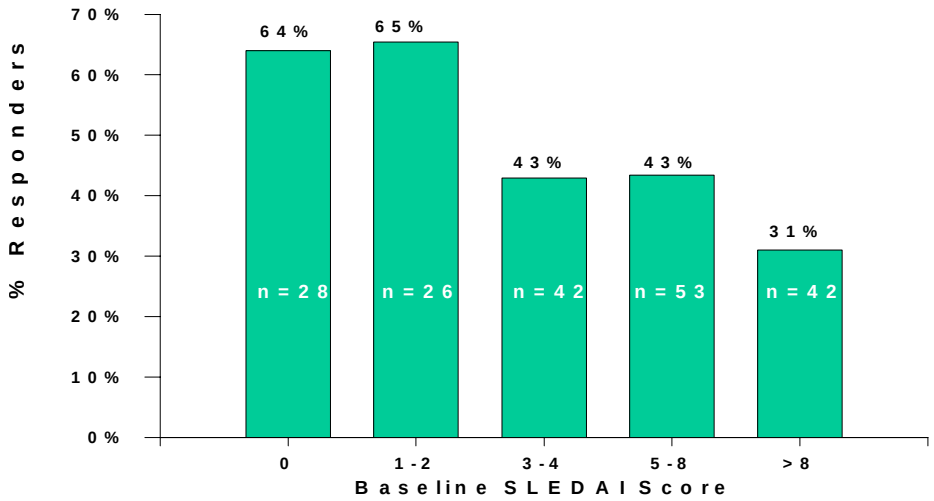


Figure 6–1: Percent Responders Based on SLEDAI Score

Based on these findings, in March 1997, FDA agreed to a proposal for prospectively (i.e., prior to breaking the blind) defining a subgroup of patients with active disease, i.e., patients with baseline SLEDAI > 2 as part of the efficacy analysis in that study was made. The data base was finalized and locked in April 1997, the study analyzed and a final report submitted to the FDA in October 1997.

6.1.2 Entry Criteria

Study patients were women with mild to moderate corticosteroid-dependent SLE, characterized by chronic treatment with prednisone 10 - 30 mg/day and either a) in the last 12 months attempted to taper prednisone dose but failed and had a stable prednisone dose for at least 6 weeks preceding the study, or b) in whom there had been no attempt to taper in the last 12 months and had been on a stable prednisone dose for at least 3 months preceding the study. Patients receiving immunosuppressive medications were excluded from the study.

6.1.3 Study Activities

Patients returned at monthly visits for up to 7 to 9 months. At each visit, assessments included SLEDAI, KFSS, SF-36, Patient VAS and Physician VAS. Corticosteroid dose was to be reduced by an algorithm: Prednisone dose (or its equivalent in other corticosteroids) was reduced if disease activity was stable or improved by SLEDAI score (SLEDAI score remained the same or decreased in comparison to the previous monthly visit). Prednisone was tapered according to the following schedule:

If daily prednisone dose was:	Dose reduction was:
>0 – ≤ 5 mg	1 mg/day
>5 mg – ≤ 10 mg	2.5 mg/day
>10 mg – ≤ 30 mg	5.0 mg/day
> 30 mg	Taper at Investigator's discretion

If the SLEDAI score had worsened (increased) since the prior monthly visit, the daily dose of prednisone could be increased at the investigator's discretion. Thus, while patients who received baseline prednisone doses > 30 mg were excluded from participation in the study, patients could receive a prednisone dose > 30 mg during the course of the study if medically indicated.

6.1.4 Patient Populations for Analysis

The primary population for analysis of efficacy was defined as all randomized patients (i.e., the intent-to-treat population). Additionally, as described above, patients with baseline SLEDAI >2 were a predefined group for analysis, and therefore analyses are presented for all patients and for patients with baseline SLEDAI > 2.

6.1.5 Efficacy Variables

A responder was defined as a patient who achieved a decrease in prednisone dose to 7.5 mg/day or less, sustained for no less than three consecutive scheduled visits, including the termination visit (i.e., two consecutive months), on or after the Month 7 Visit. If a patient achieved a lowering to 7.5 mg/day or less at Visit 6 or 7, but if she had not been at this dose for 2-months, then the patient could remain on study an additional 1 to 2 months.

A second efficacy variable was the percent decrease in prednisone dose comparing the prescribed prednisone (or steroid equivalent) dose at Baseline (Qualifying Visit) and the last visit prednisone (or steroid equivalent) dose. Additional efficacy variables included mean changes from baseline for the SLE scoring instruments and number days prednisone dose was ≤ 7.5 mg.

6.1.6 Study Patient Population and Demography Results

The study population of 191 patients consisted of women, primarily Caucasian (60%) and African-American (26%). Key demographic and baseline characteristics are summarized in **Tables 6-1 and 6-2**. There were some differences between the groups, though none was statistically significant. Baseline mean DHEA-S levels were much higher in the GL701 200 mg group. However, this probably represents the effect of three patients with very high levels, which may be attributed to laboratory error or treatment with DHEA from another source: these patients had baseline levels of 2608, 1345, and 264 μg/dl. The standard deviation for the GL701 200 mg group was 364.73, and the median values were similar in all three groups.

Mean and median prednisone dose was highest in the placebo group (15.2 and 15.0 mg/day) and lowest in the GL701 200 mg group (13.7 and 10.0 mg/day), but the difference was not significant among the three groups ($p = 0.178$).

Among the patients with baseline SLEDAI > 2, the treatment groups showed similar small differences in demographic and baseline characteristics, but the imbalance in baseline mean prednisone dose was significant among the three treatment groups ($p = 0.039$).

Table 6-1: Demographic Characteristics (GL94-01)

	All Patients			Baseline SLEDAI >2		
Parameter	**Placebo N = 64**	**GL701 100mg N = 63**	**GL701 200mg N = 64**	**Placebo N = 45**	**GL701 100mg N = 47**	**GL701 200mg N = 45**
Mean (Median) Age	41 (39)	40 (39)	40 (41)	41 (39)	39 (39)	40 (41)
Caucasian	44 (69%)	36 (57%)	35 (55%)	31 (69%)	26 (55%)	23 (51%)
African-American	17 (27%)	16 (25%)	17 (27%)	12 (27%)	12 (26%)	11 (24%)
Hispanic	0 (0%)	8 (13%)	9 (14%)	0 (0%)	6 (13%)	9 (20%)
Post-Menopausal	21(33%)	21 (33%)	12 (19%)	17 (38%)	15 (32%)	10 (22%)
Pre-Menopausal	43 (67%)	42 (67%)	52 (81%)	28 (62%)	32 (68%)	35 (78%)

Table 6-2: Baseline Characteristics (GL94-01)

	All Patients			Baseline SLEDAI >2		
Parameter	**Placebo N = 64**	**GL701 100 mg N = 63**	**GL701 200 mg N = 64**	**Placebo N = 45**	**GL701 100 mg N = 47**	**GL701 200 mg N = 45**
DHEA-S Mean (Median) µg/dl	29.0 (22.0)	28.9 (17.0)	86.5 (18.0)	29.1 (22.0)	32.3 (17.0)	116.4 (18.0)
Prednisone Dose, Mean (Median) mg/d	15.2 (15.0)	13.7 (12.5)	13.7 (10.0)	15.7 (15.0)	13.6 (12.5)	13.0 (10.0)
Antimalarial Use (%)	33 (51.6%)	27 (42.9%)	33 (51.6%)	21 (46.7%)	15 (31.9%)	22 (48.9%)
SLEDAI Score, Mean (Median)	6.4 (4.0)	5.5 (4.0)	5.9 (6.0)	8.7 (7.0)	7.0 (6.0)	8.1 (6.0)
Patient VAS, Mean (Median)	49.1 (48.5)	46.4 (47.0)	46.8 (47.5)	51.7 (55.0)	46.4 (47.0)	46.4 (49.0)
Physician VAS, Mean (Median)	28.0 (23.0)	26.0 (24.0)	23.3 (21.5)	34.6 (33.0)	29.4 (28.0)	28.5 (26.0)
KFSS, Mean (Median)	5.3 (5.7)	5.1 (4.9)	5.4 (5.7)	5.3 (5.9)	5.0 (4.9)	5.3 (5.4)

6.1.6.1 Patient Disposition

The proportion of patients discontinuing study for any cause was similar in all three treatment groups (**Figure 6-2**). More than 70% of patients in each treatment group completed the study.

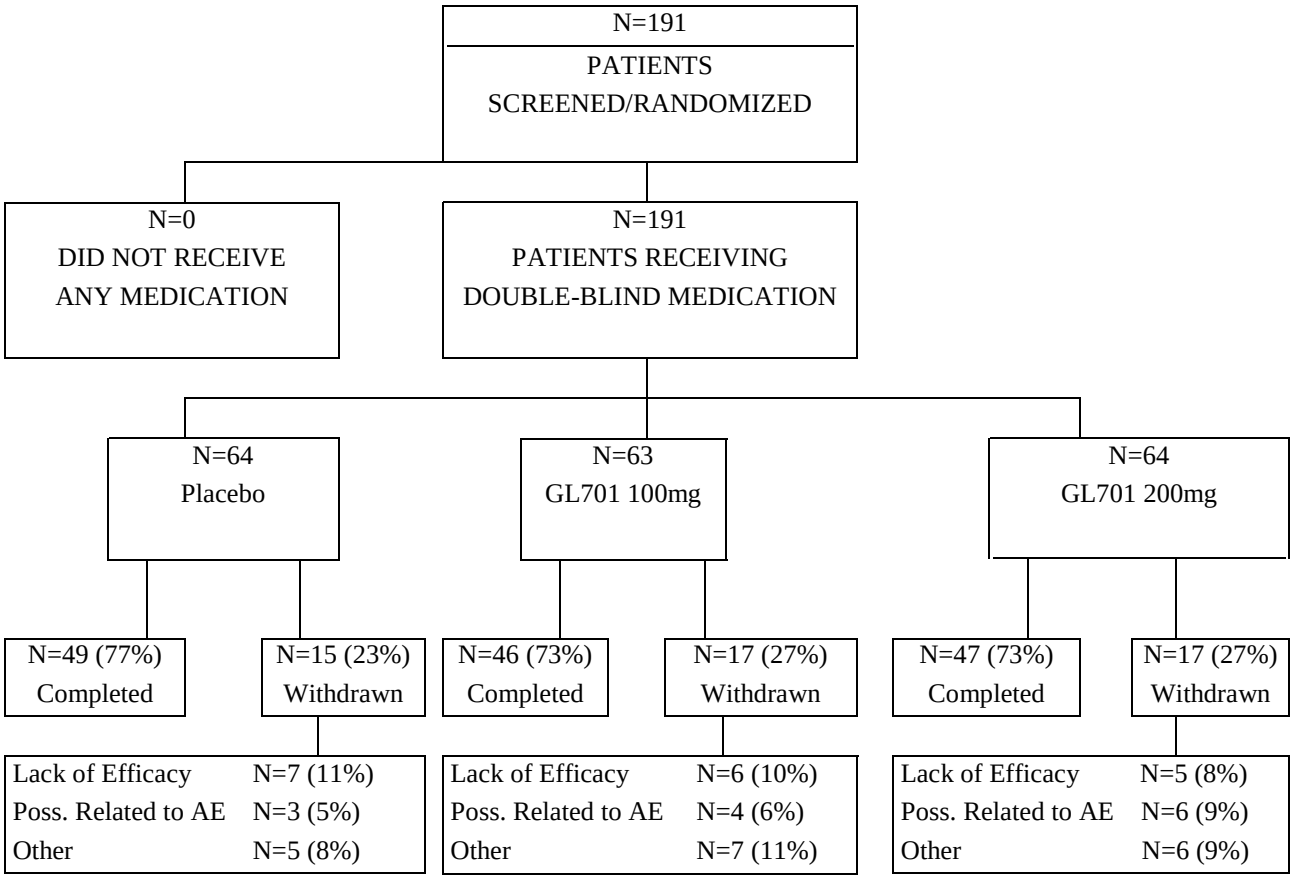


Figure 6-2: Disposition of Patients

6.1.7 Dosing Information

As shown in **Table 6-3**, mean and median duration of study drug treatment were similar in the three treatment groups.

Table 6-3: Total Days on Drug by Treatment Group

	N	Mean ± SD	Median	Range
Placebo	64	172.3 ± 54.62	196.0	2 - 236
GL701 100 mg	63	175.7 ± 50.43	195.0	7 - 232
GL701 200 mg	64	177.4 ± 45.66	194.5	12 - 224

6.1.8 Efficacy Results

6.1.8.1 Primary Efficacy Variables

A. Proportion of Patients Achieving Sustained Prednisone Reduction

The primary efficacy variable was the achievement of a decrease in actual prednisone dose to ≤7.5 mg/day sustained for at least three consecutive scheduled visits including the termination visit (i.e., two consecutive months). Due to the nature of SLE, it was considered important to have a response of meaningful duration. Patients who achieved this sustained prednisone dose reduction were defined as responders. As noted earlier, prednisone reduction was determined according to a SLEDAI based algorithm; prednisone could be reduced at monthly visits if the SLEDAI was stable or reduced at each consecutive visit.

For all randomized patients, there was a strong trend in favor of GL701 200 mg (P=0.110 vs. placebo). For patients with baseline SLEDAI > 2, the difference between placebo and GL701 200 mg was significant (p= 0.031) and there appeared to be a dose response relationship (p=0.033 for linear trend).

When patients with SLEDAI $\leq$ 2 are analyzed separately, there is a high response rate in all three treatment groups (68%, 63%, and 63%), consistent with the possibility that many patients who entered the study with SLEDAI $\leq$ 2 were more likely to have inactive SLE and not truly steroid dependent. That is, their steroid doses could be reduced to 7.5 mg/day, regardless of treatment group, without worsening of disease.

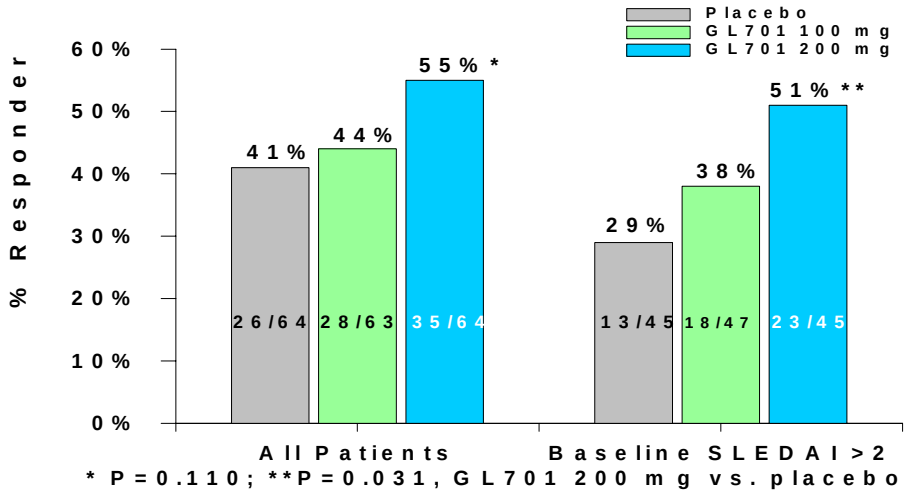


Figure 6-3: Percent Responders

Examination of the SLEDAI descriptors for patients with baseline SLEDAI $\leq$ 2 confirmed that such patients were more likely to have inactive disease. Of the 54 patients with baseline SLEDAI scores $\leq$ 2 the SLEDAI descriptors were consistent with clinically active SLE in only 6 (11%) patients. These were patients with pleurisy, rash, alopecia, mucosal ulcers, or leukopenia, which resulted in SLEDAI scores of 1 or 2. In the remaining 48 patients, the SLEDAI scores were not consistent with clinically active SLE. In 28 of these 48 patients, the SLEDAI score was 0, suggesting no measureable disease activity; and in 20 of these 48 patients, the SLEDAI score of 1 or 2 represented only serologic findings: 18 patients with increased DNA binding and 2 patients with decreased complement, both of which can remain positive regardless of clinical disease activity (Urowitz, 1999).

The pattern of responders was further explored by examining the proportion of patients who had reached a daily prednisone dose of ≤ 7.5 mg/day at each monthly visit (**Figure 6-4**). The percentage of patients who achieved a prednisone dose of ≤ 7.5 mg/day in the GL701 200 mg group was higher than placebo at all time points.

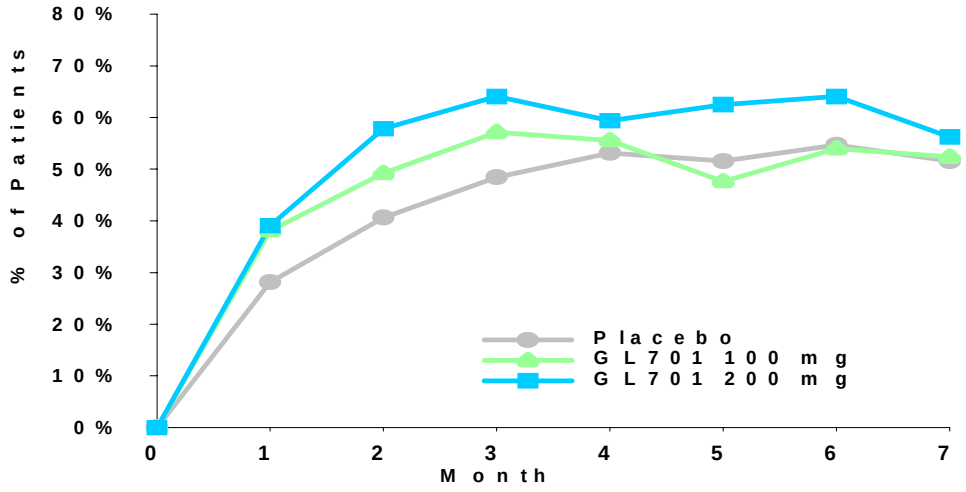


Figure 6-4: Percent of Patients with Prescribed Prednisone Dose ≤ 7.5 mg/d

As shown in **Figure 6-5**, in patients with baseline SLEDAI >2, the percent of patients who achieved a prednisone dose of ≤ 7.5 mg/day in the GL701 200 mg group was also higher than placebo at all time points. Approximately 60% of the GL701 200 mg group with baseline SLEDAI score >2 achieved a daily prednisone dose of ≤ 7.5 mg at Visits 3 through 6 compared with approximately 40% of the placebo treated patients. A possible confounding factor is that the prednisone dose at baseline was higher in the

placebo group, median 15.0 mg/day compared to 10.0 mg/day in the GL701 200 mg group. However, this imbalance in baseline prednisone dose would have delayed the achievement of a dose of 7.5 mg/day by only one or two months in the placebo group since the downward titration algorithm required a decrease of 5 mg/day for doses $\geq$ 10 mg/day.

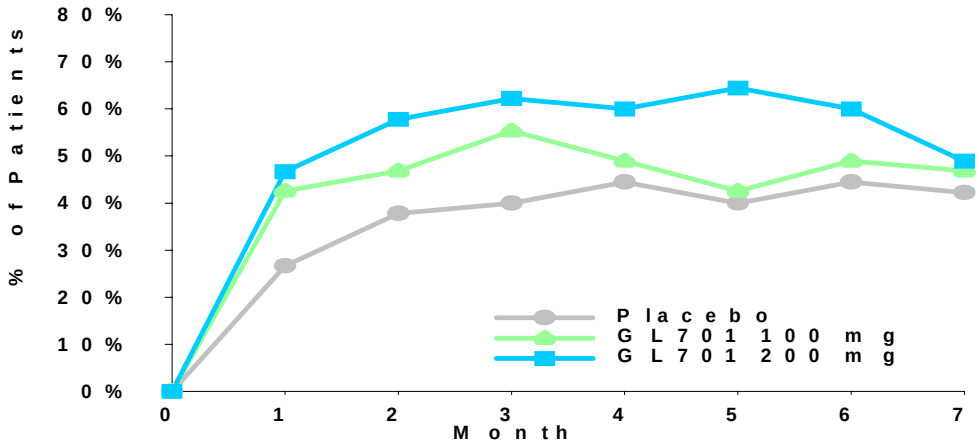


Figure 6-5: Precent of Patients with Prescribed Prednisone Dose ≤ 7.5 mg/d Baseline SLEDAI >2

A.1 Effect of Baseline Prednisone Dose

Because there was a statistically significant imbalance in baseline prednisone dose among treatment groups for patients with baseline SLEDAI >2, prednisone dose was categorized in order to determine responder rates among patients having similar baseline prednisone dose. In this tabulation, the responder rates for the three treatment groups are compared within low and high baseline prednisone dose categories, allowing a direct comparison of the three treatment groups within a baseline prednisone dose category (**Table 6-4**).

Table 6-4: Responder Rate by Treatment Category and by Prednisone Dose Subcategory Patients with Baseline SLEDAI > 2 (GL94-01)

Treatment	Baseline Prednisone Dose					
	10 mg to 15 mg			> 15 mg to 30 mg		
	No. of Patients	No. of Responders	%	No. of Patients	No. of Responders	%
Placebo	30	11	36.7	15	2	13.3
100 mg	39	17	43.6	8	1	12.5
200 mg	38	21	55.3	7	2	28.6

In the low baseline prednisone dose (≤ 15 mg) group, where there are enough patients (30 to 39 per treatment group) to estimate responder rates, there was a strong trend in favor of GL701 200 mg over placebo, placebo 37% vs. GL701 200 mg 55%, representing an approximate 50% increase in responders. In the high baseline prednisone group (> 15 mg), the trend was still present, with placebo 13% vs. GL701 200 mg 29%, representing an approximate 53% increase in responders over placebo; but there were fewer patients (7 to 15 patients per treatment group).

B. Mean Percent Decrease in Prednisone Dose at the Last Visit

A second efficacy variable was mean percent decrease in prednisone use, comparing final dose with baseline. The mean (SD) and median percent changes (from baseline to last visit) in prescribed prednisone dose are listed below, by treatment group in **Table 6-5**:

Table 6-5: Mean Percent Change from Baseline to Last Visit in Prescribed Prednisone Dose (GL94-01)

	Treatment Group		
	Placebo N = 64	GL701 100 mg N = 63	GL701 200 mg N = 64
Mean (SD) % Change	-35.8 (50.2) %	-13.7 (91.4) %	-30.3 (74.3) %
Median % Change	-50.0%	-41.2%	-52.5%
P-value for Mean Percent Change, GL701 vs. Placebo		0.094	0.672

While no statistically significant differences were detected for each of the pairwise comparisons (active treatment vs. placebo), this endpoint only assessed prednisone dose on the last day of treatment rather than the durability of prednisone reduction, i.e. the ability to maintain a sustained reduction of prednisone for at least 2 months. In some patients who achieved a dose of 7.5 mg/day and remained stable or improved, their prednisone dose was further reduced, in some cases as low as 2 or 0 mg/day, which may have caused them to flare. Because an algorithm for prednisone increase was not stipulated in the

protocol, analysis of prednisone dose only on the last study day was of limited utility in characterizing steroid reduction.

Therefore, prednisone reduction was further explored by analyzing the number of days with prednisone dose ≤ 7.5 mg by treatment group for all randomized patients and for those with baseline SLEDAI >2 (**Table 6-6**). Although this was a post hoc analysis, it provides an additional quantitative measure of the primary efficacy variable of steroid sparing that is not impacted by just the last day on study.

Table 6-6: Days Prednisone Dose ≤ 7.5 mg

Treatment	Mean Days (SD)	Median Days	P value[1]
All Randomized Patients			
Placebo (N=64)	71.7 (65.5)	66.5	
GL701 100 mg (N=63)	77.7 (63.2)	81.0	N.s.
GL701 200 mg (N=64)	92.1 (65.5)	111.5	0.069
Baseline SLEDAI > 2			
Placebo (N=45)	59.7 (65.5)	28.0	
GL701 100 mg (N=47)	74.0 (63.5)	55.0	N.s.
GL701 200 mg (N=45)	93.4 (66.4)	111.0	0.013

1. GL701 vs placebo, Wilcoxon Rank-Sum test

The number of days daily prednisone dose was 7.5 mg/day or lower were greater in the GL701 200 mg group. In the subgroup baseline SLEDAI > 2, the number of days prednisone dose was < 7.5 mg/day was also significantly reduced for GL701 200 mg in comparison to placebo.

6.1.9 SLE Scoring Instruments

The secondary efficacy variables included change from baseline in the measurements of the following: SLEDAI, SF36, KFSS, Physician VAS and Patient VAS. In both groups measures of SLE activity remained stable. There was no significant change in any of the scores, as well as no statistically significant differences between treatment groups for changes in any of these variables from baseline. As noted earlier, this was expected, as the main purpose of the trial was to reduce prednisone dose without causing worsening of disease. This was to be accomplished by a forced titration, based on the SLEDAI score at each visit. Therefore, only stabilization of disease rather than improvement, as measured by the different scores, would be expected; and the critical difference between treatment groups would be expected to be found in the proportion of patients successfully achieving steroid reduction.

6.1.10 Study GL94-01 Conclusion

In summary, more GL701 patients than placebo patients were responders: i.e., achieved sustained prednisone reduction without worsening of signs and symptoms of SLE. This difference approached significance in the intent-to-treat patients and achieved significance in those with baseline SLEDAI > 2. There was a dose-response relationship, with the numbers of responders in the GL701 group being intermediate between GL701 200 mg and placebo. The difference in responders appeared early in the study and was maintained for the duration of the study. Although mean decrease in prednisone dose on the last day of study was not different between the groups, the mean number of days with a daily dose of prednisone $\leq$ 7.5 mg was significantly greater in the GL701 200 mg group.

6.2 STUDY GL95-02 (IMPROVEMENT IN SLE)

Study GL95-02 was a Phase III study which compared the proportion of patients achieving improvement or stabilization of the signs and symptoms of SLE. The treatment phase was 12 months.

6.2.1 Protocol Development

Because of lack of previous experience or guidelines for clinical trials in SLE, the design and analysis of study GL95-02 was a collaborative effort between the sponsor and FDA. At a meeting with FDA in November 1995, key critical design features of this protocol, which differed significantly from the design of GL94-01, were discussed. The primary efficacy variable, developed in collaboration with FDA specifically for this study, was the proportion of patients who are "responders." A "responder" was defined as a patient who satisfied the following conditions:

1. The patient had to have improvement or stabilization in two disease activity assessments (i.e., SLAM, SLEDAI), and two patient assessed outcomes (i.e., Krupp Fatigue Severity Scale [KFSS], Patient Global Assessment by Visual Analogue scale [Patient VAS]) based on the available on-treatment data. Improvement or stabilization meant that to be a responder, for each of the four scoring instruments, the mean of all on-treatment visits had to be the same as or less than the mean of the baseline visits.

2. A patient could not have clinical deterioration. Clinical deterioration was defined as the occurrence of serious new or progressive lupus-related conditions or requirement for unacceptable increase in immunosuppressive or cytotoxic therapy for lupus while the patient received study drug (refer to **Appendix 2** for a detailed description).

One issue identified with the responder definition was that the exact numerical definition of stabilization or "the same as" was not specified. Because of the considerable inherent variability in these instruments, at a November 1995 meeting with FDA, the need for a tolerance window was discussed. It was suggested that stabilization be defined as occurring when the difference between mean of baseline and mean of on-treatment visits allowed for a certain "tolerance window" i.e., a difference equal to zero plus/minus a certain amount of variability. The issue was not resolved at this meeting.

One of the important eligibility criteria was that patients have active, but relatively stable disease. To accomplish this, patients were required to have a SLAM score of $\geq$ 7 and had to be receiving stable doses of medications such as prednisone, immunosuppressives, cytotoxics and antimalarials; and maximum corticosteroid dose at baseline had to be $\leq$ 10 mg/day of prednisone or its equivalent and unchanged for $\geq$ 6 weeks prior to study entry. At the time, there was considerable discussion whether the SLAM or SLEDAI score should be used as a criterion for determining active disease. The SLAM score was finally chosen because it was thought that it would be more sensitive to identify disease in this patient population, assumed to have mild disease due to the requirement for no more than 10 mg/day prednisone. There was, however, concern that the SLAM score was too sensitive to mild subjective complaints.

In July 1997, the findings in Study GL94-01 regarding the importance of baseline SLEDAI >2 as an indicator of active SLE were also discussed with FDA. At that time approximately 290 patients had been enrolled. Based on these discussions, in August 1997 the protocol for GL95-02 was amended to require baseline SLEDAI > 2 as an additional enrollment criterion of active SLE allow the enrollment of at least 50 additional patients meeting that criterion.

When the final report for Study GL94-01 was discussed with FDA in November 1997, FDA suggested that the findings with regard to baseline SLEDAI >2 were a hypothesis, which should be confirmed in Study GL95-02.

During the clinical development process additional important features of the analysis plan for Study GL95-02 were discussed and finalized.

6.2.1.1 Primary Population and Handling Missing Values

The original protocol (January 31, 1996) had specified that "All randomized patients will be analyzed in an intent-to-treat analysis." However, how patients with missing values should be treated was not specified. This made the analysis of the primary endpoint, responder, ambiguous because the responder definition specified that for each of the 4 scoring instruments "the value of interest for each patient"

would be the difference between the baseline means and "the mean of all values during on-treatment scheduled visits". If a patient did not return for at least her first visit, (not scheduled until after 90 days on treatment), and consequently had no post-baseline assessments, the protocol did not specify how she should be evaluated as a responder or non-responder. Accordingly, in an analysis plan submitted to FDA in October 1998, and discussed at a November 1998 meeting, Genelabs proposed that the population for analysis be defined as all randomized patients with at least one post-baseline measurement (per protocol population) and at least 60 days of study drug treatment.

Per FDA's request, a more detailed analysis plan was submitted as an IND amendment in July 1999. The analysis plan specified that the primary population for analysis of efficacy would be the per-protocol population: those patients who had been on the study drug for more than 60 days and had had at least one post-baseline measurement beyond 60 days. An intent-to-treat population was defined as all randomized patients. The justification for requiring a minimum of > 60 days exposure to study drug for the primary analysis of efficacy was based on the fact that the first scheduled visit was at 90 days and the need for a minimal treatment period required for effectiveness. This minimal treatment period was discussed at a protocol planning meeting in September 1995, and eventually was included as part of the definition of clinical deterioration. In this proposal, those patients without post-baseline assessments would be excluded from the primary analysis of efficacy, consistent with the three criteria described in the final FDA guidance document "E9 Statistical Principles for Clinical Trials," *Per-Protocol Set: (i) completion of certain pre-specified minimal exposure to treatment regimen; (ii) availability of the primary variable(s), and (iii) absence of any major protocol violations*. However, in the intent-to-treat population, patients without post-baseline assessments would, by default, be considered as non-responders.

6.2.1.2 Handling Inter-Intrarater Variability in the Composite Endpoint

At the same meeting in November 1998, as noted above, the issue of a range of tolerances or a "window" for stabilization was proposed in a more formal manner in the draft analysis plan. The tolerance range was proposed as ±0.5 for the SLEDAI and KFSS, ±1 for the SLAM and ±10 for the patient VAS. Additionally, because of concern about the lack of previous experience with the primary efficacy endpoints, an additional secondary efficacy endpoint, proportion of patients with flare, was proposed. The FDA noted that additional analyses that might better capture clinical successes may be performed and that the overall pattern of the data would be important.

After obtaining agreement from FDA regarding the missing value proposal, the statistical analysis plan was finalized prior to breaking the blind. The process by which the analysis plan was finalized is

consistent with the expectations set forth in the guidance document, "E9 Statistical Principles for Clinical Trials," *Section V. Data Analysis Considerations, 5.1 Prespecification of the Analysis*.

6.2.2 Entry Criteria

The study population was restricted to women with active, mild to moderate SLE. Active SLE was defined, as SLAM score $\geq$7 (excluding ESR), and later in a protocol amendment, SLEDAI score >2 was added as an additional enrollment criterion. Mild to moderate was defined as patients receiving no prednisone or up to 10 mg/day (or its equivalent of other corticosteroids).

6.2.3 Study Activities

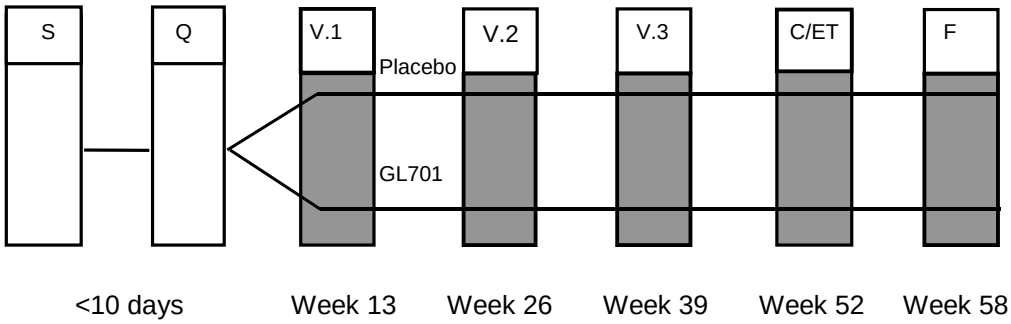
Patients were randomly assigned to receive 200 mg/day GL701 or placebo. Patients remained on the same blinded treatment for the duration of the study. Following the Screening/Qualifying period, patients were to return to the clinic at Weeks 13, 26, 39, and 52 (Completion Visit), or, if necessary, at an Early Termination Visit followed by a 6-week early termination or completion visit and adverse event follow-up assessment by telephone.

Concomitant medications, including NSAIDs, glucocorticoids, antimalarials, and immunosuppressives had to have been stable for at least 6 weeks prior to enrollment. The investigators and the patients' physicians were to make all reasonable efforts not to change the dosage of these medications during the study. Patients could not be receiving more than 10 mg/day of prednisone (or glucocorticoid equivalent) at baseline.

Scheduled visit evaluations included physical examinations, laboratory determinations, SLAM determination, 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), American College of Rheumatology (ACR) criteria at baseline and the SLICC (Systemic Lupus International Cooperating Clinics) Damage Index at baseline and study Completion/EarlyTermination.

Eight investigators also assessed bone mineral density by dual energy x-ray absorptiometry (DEXA) scans in patients who had received steroids for at least 6 months prior to study entry.

The study plan is shown below in **Figure 6-6.**



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

Figure 6-6: GL95-02 Study Plan

6.2.4 Patient Populations for Analysis

As described above in **Section 6.2.1 Protocol Development**, the protocol was amended to also require baseline SLEDAI > 2 as an entry criterion. Additionally, in the detailed analysis plan, the primary data set for analysis of efficacy was specified as the per-protocol population.

Therefore, generally all analyses are presented for the per-protocol population and for patients with baseline SLEDAI >2. For analysis of responders, these analyses are presented using the range of tolerance described above. An ITT analysis of efficacy has also been performed as described in the original protocol (January 1996). Additionally, results for the modified ITT (i.e. full dataset for analysis) are also provided for comparison purposes.

6.2.5 Primary Efficacy Variables

A. Proportion of Patients Improved or Stabilized

The primary efficacy variable or endpoint was responder, a per-patient endpoint that integrated three domains of SLE: disease activity, as measured by the SLEDAI and SLAM; quality of life or constitutional symptoms, as measured by the patient VAS and KFSS; and organ damage, as assessed by clinical deterioration. A responder had to demonstrate improvement or stabilization of each of the above four scoring instruments and also, not experience "clinical deterioration."

"Clinical deterioration" was defined as occurring for any of the following reasons: 1) serious drug toxicity attributable to study drug or other SLE therapy, or 2) serious new or progressive SLE manifestations, or 3) requirement for substantial increase in prednisone (>5 mg/day for at least two consecutive months) or new/increased immunosuppressive therapy for SLE.

Improvement or stabilization in each of the scores was prospectively defined as the time-weighted mean of all on-treatment visit measurements being less than or equal to the mean of the baseline values. As discussed previously, stabilization was not precisely defined in the original protocol, but remained under discussion. In the analysis plan for this study, the sponsor proposed putting a range of tolerance values or a "window" around this difference for each of the four scores, so that inherent test-retest variability in scoring the instruments would not cause a patient to be classified as a non-responder.

The tolerances proposed at the November 1998 meeting with FDA were ±0.5 for the SLEDAI and KFSS, ±1 for the SLAM and ±10 for the patient VAS. The assignment of these values were based both on the reported variability and on the different scales of these scoring instruments, which range from 1 to 7 for the KFSS, 0 to 100 for the Patient VAS, 0 to 105 for SLEDAI, and 0 to 86 for the SLAM. Copies of these four instruments are provided in **Appendix 1**.

Such instrument-related variability has been studied and reported for the SLEDAI, SLAM, Patient VAS, as well as other instruments, by a number of investigators. For example, DeLoach et al, (1998) found a 20 mm retest difference in the Patient VAS. Other investigators have reported similar or greater variability for the SLEDAI, SLAM, and physician and patient VAS (Liang, 1989; Bombardier, 1992; Petri,1992; Fitzgerald and Grossman, 1999)

6.2.6 Secondary Efficacy Variables

A. Flare

A secondary efficacy variable was "flare." This efficacy variable was defined towards the end of Study GL95-02 with concurrence from FDA. A "definite flare" was defined as: at least one of the following SLE descriptors and/or interventions. The descriptor must be a significant new (not present at previous visit) clinical finding.

New/worse CNS Lupus	Must be scored on SLEDAI and not present on previous visit.
Vasculitis	Must be scored on SLEDAI and not present on previous visit.
Myositis	Must be scored on SLEDAI and not present on previous visit.
Hematologic	Platelets < 60,000 or hemoglobin < 7mg/dl or decrease of at least 3 mg/dl.
Nephritis	Proteinuria with pyuria and/or hematuria treated with new/increased dose of corticosteroids or immunosuppressives.
Steroids	An increase of ≥ 2.5 mg for at least 7 days for SLE related reasons.
Immunosuppressives or Antimalarials	New use of or increase in dose for at least 7 days for SLE related reasons.
Hospitalization	Hospitalization for new SLE manifestation

The definition of flare was developed with a number of the investigators participating in GL95-02, and was a modification of the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) definition of flare (Petri, 1999).

B. Other Secondary Efficacy Variables

Additional secondary efficacy variables included: change from baseline for scoring instruments for each of the following scores: SLAM, SLEDAI, Patient VAS, KFSS, Physician VAS, SF-36, SLICC, and percent change in DEXA.

6.2.7 Study Patient Population and Demography Results

6.2.7.1 Patient Population and Demography

The important demographic features and baseline characteristics are summarized in **Tables 6-7** and **6-8** for the per-protocol population and in **Appendix 3** for the intent-to-treat population. There were no clinically meaningful or statistically significant differences between treatment groups for any of the baseline demographic characteristics in either the per-protocol or intent-to-treat populations. Additionally, there were no meaningful differences between treatment groups for patients with baseline SLEDAI > 2.

Table 6–7: Demographic Characteristics (GL95-02)

	Placebo N=176	GL701 N=170	Placebo N=133	GL701 N=132
Parameter	**Per Protocol**		**Per Protocol, Baseline SLEDAI > 2**	
Mean (Median) Age	44 (43)	44 (44)	44 (43)	44 (43)
Caucasian	125 (71%)	132 (78%)	90 (68%)	100 (76%)
African-American	31 (18%)	21 (12%)	25 (19%)	17 (13%)
Hispanic	15 (9%)	12 (7%)	13 (10%)	11 (8%)
Post-Menopausal	86 (49%)	74 (44%)	63 (47%)	57 (43%)
Pre-Menopausal	90 (51%)	96 (57%)	70 (53%)	75 (57%)

Table 6–8: Baseline Characteristics (GL95-02)

	Placebo N=176	GL701 N=170	Placebo N=133	GL701 N=132
Parameter	**Per Protocol**		**Per Protocol, Baseline SLEDAI > 2**	
DHEA-S μg/dl Mean (Median)	103 (47.3)	105.5 (61.7)	92 (41.85)	104.3 (61.87)
Prednisone Use	98 (55.7%)	91 (53.5%)	80 (60.2%)	73 (55.3%)
Mean (Median) Prednisone Dose mg/day	3.9 (3.3)	3.4 (3.0)	4.2 (5.0)	3.6 (5.0)
Immunosuppressive Use	27 (15.3%)	29 (17.1%)	24 (18.0%)	26 (19.7%)
Antimalarial Use	46 (26.1%)	41 (24.1%)	34 (25.6%)	26 (19.7%)
Mean (Median) SLEDAI	5.9 (5.0)	6.5 (6.0)	7.4 (6.0)	8.1 (8.0)
Mean (Median) SLAM	12.0 (12.0)	12.3 (12.0)	12.5 (12.0)	12.8 (12.5)
Mean (Median) Patient VAS	55.1 (57.0)	55.2 (57.0)	54.8 (56.5)	57.3 (58.5)
Mean (Median) KFSS	5.6 (5.7)	5.5 (5.9)	5.6 (5.8)	5.6 (5.9)

6.2.8 Patient Disposition

Three hundred eighty one (381) patients were randomized, of whom 346 were in the per-protocol population. Of the 35 patients not meeting the criteria for the per-protocol population, 32 had no post-baseline efficacy assessments. The other 3 were excluded because of a major protocol violation (one patient) or receiving less than 60 days study drug (2 patients). Details regarding these 35 patients are in **Appendix 4**. Fifty (26%) of the 192 placebo patients and 65 (34%) of the 189 GL701 patients discontinued study drug before 12 months (**Figure 6-7**). The difference in early withdrawals was mainly due to mild androgenic adverse events. Hirsutism and/or acne were reported as a reason for early termination in 11 (6%) of the GL701 group, compared to none of the placebo group.

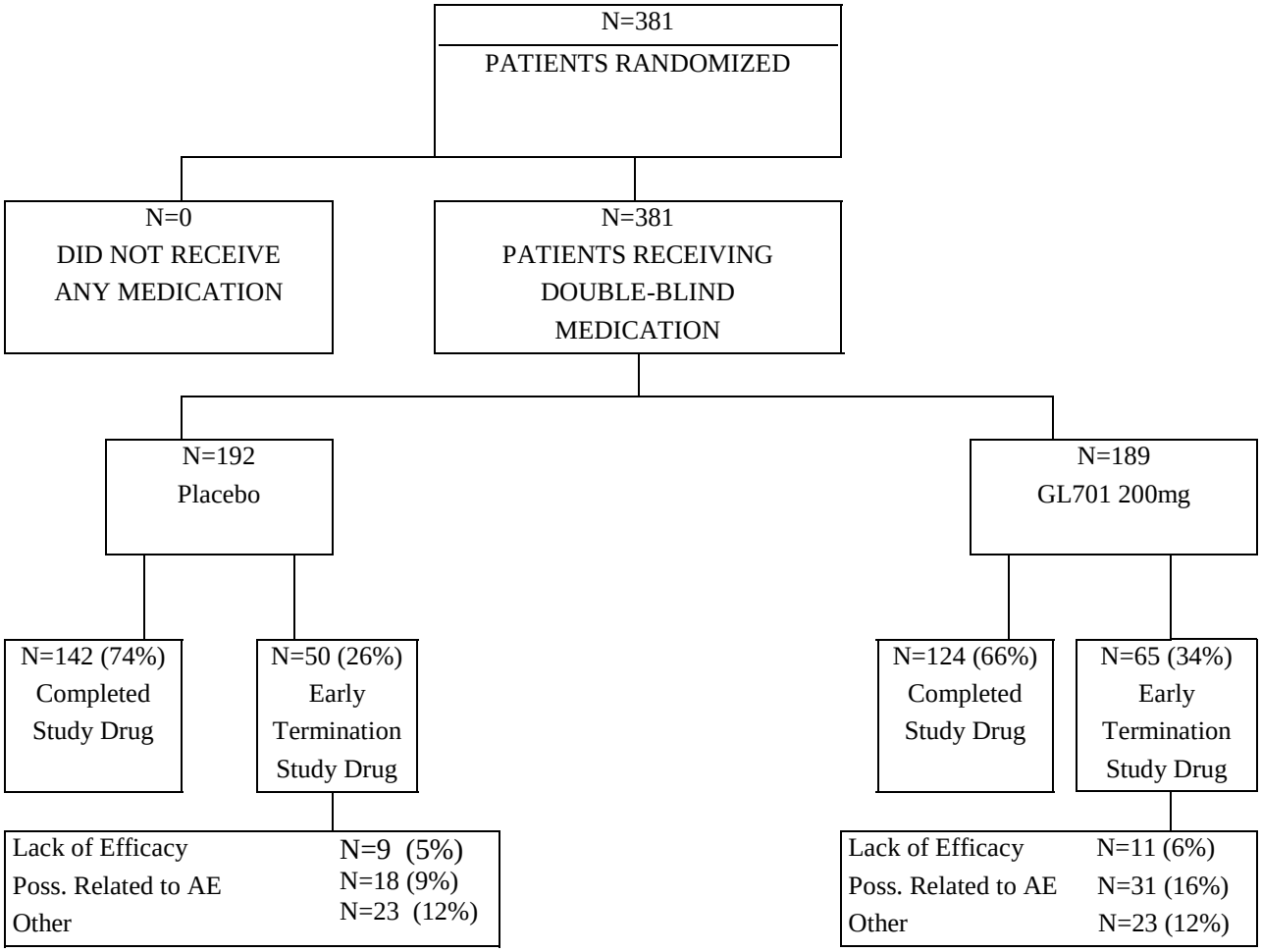


Figure 6–7: Disposition of Patients

6.2.9 Dosing Information

In the per-protocol population, mean duration of study drug treatment was somewhat longer in the placebo group, 330.3 vs 316.7 days, but median durations were almost identical, 363 vs. 361 days.

6.2.10 Efficacy Results

6.2.10.1 Primary Outcome - Response

As shown in **Figure 6-8** below, there were more responders in the GL701 group compared to the placebo group. This treatment effect of GL701 was present in the overall per protocol population (p=0.018) as well as in the baseline SLEDAI > 2 (p = 0.005) population. Based on a blind review of the data in Study GL94-01, baseline SLEDAI >2 (yes/no) was pre-determined as one of the important factors in the analysis plan for GL95-02. The treatment interaction with this factor was anticipated from the GL94-01

study results. Using a logistic regression model specified in the analysis plan, a significant ($p < 0.001$) treatment interaction with baseline SLEDAI > 2 (yes/no) was noted, confirming the findings from Study GL94-01 and supporting the decision to amend the protocol and halt enrollment of patients with SLEDAI $\leq$ 2. Additionally, these findings provide both clinical and statistical support that patients with no or minimal SLE activity (defined as SLEDAI $\leq$ 2) should be viewed separately from those with baseline SLEDAI > 2.

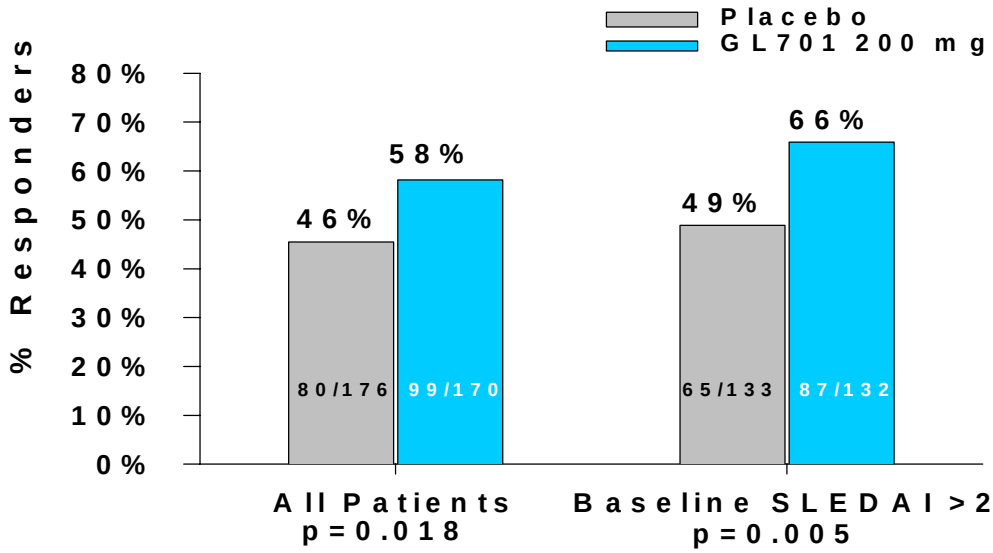


Figure 6-8: Percent Responders

The individual components of the responder definition that caused patients to be classified as non-responders were further explored in patients with baseline SLEDAI >2 (**Figure 6-9**). Slightly fewer than 10% of the patients in either treatment group met the protocol-specified criteria of clinical deterioration. However, for each of the other four criteria in the responder definition, more patients in the placebo group, compared to the GL701 group, had worsening of their SLEDAI, SLAM, KFSS, or Patient VAS scores. The greatest differences between GL701 and placebo were proportion of patients with worsening global assessment as measured by Patient VAS (p=0.008) and worsening SLEDAI (p=0.060).

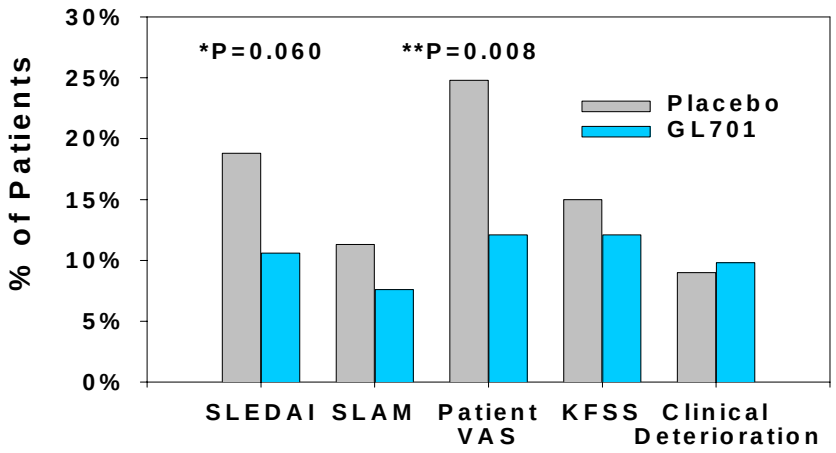


Figure 6-9: Patients not Meeting Individual Components of the Responder Definition (Baseline SLEDAI >2)

A. Validation of Use of Tolerance Window

In order to test the robustness of using a range of tolerance or "window" to decrease variability, the impact of changing the window definition was also investigated. As shown in **Table 6-9** below, which contrasts the analysis plan window with a range of arbitrarily chosen tolerance windows (i.e., 3%, 5% and 10% of the *individual patient's* baseline for each score), the results are consistent regardless of window used, with the response rate for GL701 being statistically significantly higher than placebo. Even with a tolerance of as small as 3% of baseline, the percentage of improvement in the baseline SLEDAI > 2 group is 54.4%, p = 0.002. Without a window, (i.e., 0% of the *individual patient's* baseline for each score), the percentage of improvement in the baseline SLEDAI > 2 group is similar to the analysis plan window, 34.2%, but the p value only approaches significance, p = 0.068.

Refer to **Appendix 6** for examples of individual patients that become classified as responders from non-responders using a 3% window.

Table 6-9: Evaluation of Tolerance Window: Per-Protocol Population

Variable	Per Protocol			Per Protocol Baseline SLEDAI > 2		
	Placebo N=176	GL701 N=170	P-value Improvement	Placebo N=133	GL701 N=132	P-value Improvement
Responders (No window)	52 29.5%	60 35.3%	P = 0.254 19.7%	42 31.6%	56 42.4%	P = 0.068 34.2%
Responders (Pre-defined window)	80 45.5%	99 58.2%	P = 0.018 27.9%	65 48.9%	87 65.9%	P = 0.005 34.8%
Responders (3% window)*	57 32.4%	77 45.3%	P = 0.014 39.8%	47 35.3%	72 54.5%	P = 0.002 54.4%
Responders (5% window)*	62 35.2%	79 46.5%	P = 0.034 32.1%	50 37.6%	73 55.3%	P = 0.004 47.1%
Responders (10% window)*	69 39.2%	93 54.7%	P = 0.005 39.5%	56 42.1%	85 64.4%	P = 0.001 53.0%

* baseline mean + 3%, 5%, or 10% of patient's baseline mean

In another analysis, requested by FDA, the effect of tolerance windows ranging from 3% to 30% were evaluated. As shown below in **Figure 6-10**, the difference between the GL701 and placebo responder rates is parallel and consistent with windows ranging from 3% to 30% of the individual patient's baseline for each score. These differences between GL701 and placebo are all significant except for no window (i.e., a window of 0%).

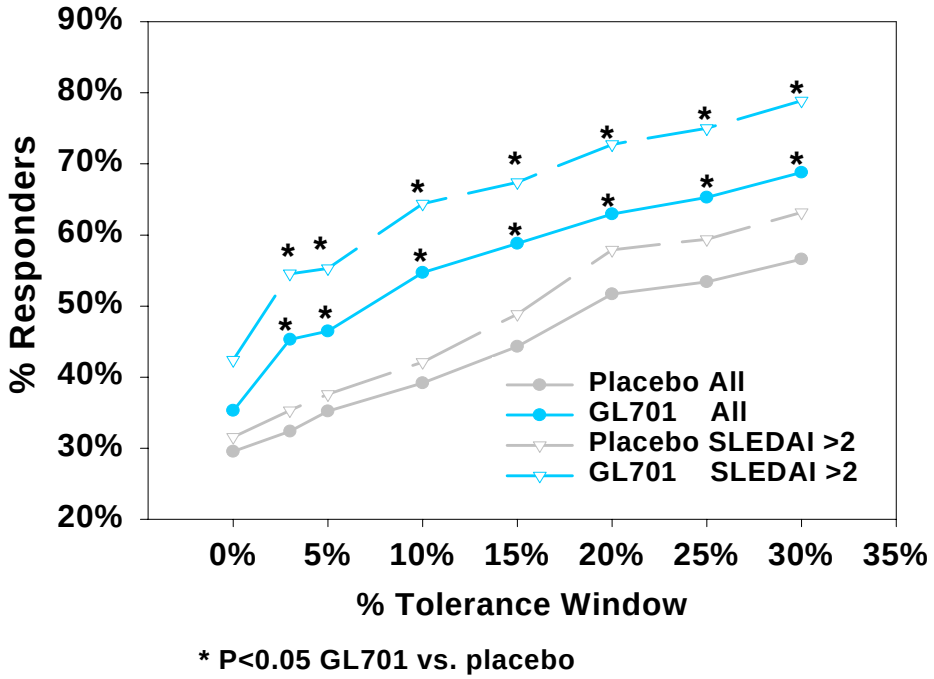


Figure 6-10: Impact of Different "Tolerance Windows"

Thus, the response rates, with or without a window, are higher in the GL701 group in comparison to the placebo group.

B. Intent-to-Treat Population

Results in the intent-to-treat population for the primary efficacy variable, responder, are presented in detail in tabular form in **Appendix 5**. In comparison to the per-protocol population, the responder rates are decreased in both GL701 and placebo groups, largely because patients without post-baseline measurements are included as non-responders. However, as in the per-protocol population, there were more responders in the GL701 group compared to the placebo group, 51.3% of 189 GL701 patients were responders compared to 42.2% of 192 placebo patients (p=0.074). It was also present in the baseline SLEDAI > 2 population, where 58.5% of 147 GL701 patients were responders compared to 44.5% of 146 placebo patients (p=0.017)

The intent-to-treat population and the per-protocol populations differed by 35 patients who were excluded from the per-protocol populations. As described in detail in **Appendix 4**, these were 32 patients without any post-baseline measurements, were assessed by default, as non-responders; and 3 patients, all in the placebo group, excluded because of a major protocol violation (1 patient) and less than 60 days study

drug treatment (2 patients). These 3 patients, who did have post-baseline measurements, could be assessed for response. One of the 3 was a responder. If responders are analyzed in a so-called modified intent-to-treat population (i.e., defined as the full set analysis according to ICH guidance), excluding the patients without post-baseline assessments, the results and p-values are almost identical to the results for the per-protocol population: 57% of 171 GL701 patients were responders compared to 45% of 179 placebo patients (p = 0.032). It was also present in the baseline SLEDAI > 2 population, where 65% of 133 GL701 patients were responders compared to 48% of 135 placebo patients (p = 0.007).

C. Comparison of Mean Changes in Scoring Instruments by Treatment Group

In general, there was improvement for the SLE scoring instruments regardless of treatment group, as measured by the mean change from baseline. The within-group change from baseline was statistically significant for all instruments, the only exceptions being the SLICC scores for both treatment groups, and SF-36 physical component score and the Patient VAS in the placebo group. Additionally, the mean improvement for the GL701 group was greater than the placebo group for each instrument, but only the difference between GL701 and placebo for Patient VAS approached significance (p=0.057 for comparison between groups, baseline SLEDAI > 2).

Table 6–10: Mean changes in scoring instruments from baseline

Variable	Per-Protocol		Per-Protocol Baseline SLEDAI > 2	
	Placebo N=176	**GL701 N=170**	**Placebo N=133**	**GL701 N=132**
Responder Components				
SLEDAI	-1.72	-2.24	-2.57	-3.17
SLAM	-2.65	-3.10	-2.63	-3.16
Patient VAS	-4.35	-6.24	-2.85	-7.22
KFSS	-0.39	-0.33	-0.27	-0.32
Other Scoring Instruments				
Physician VAS	-5.19	-5.64	-4.52	-5.38
SLICC	-0.05	-0.08	-0.06	-0.09
SF36 – MCS*	1.80	2.64	1.64	2.33
SF36 – PCS**	1.71	1.76	0.90	1.87

*Mental component score
**Physical component score

D. SLE Flares

Fewer patients in the GL701 group experienced a definite flare (see **Section 6.2.6** above for definition of definite flare): 31 (23.5%) of 132 GL701 patients had at least one definite flare compared to 41 (30.8%) of 133 placebo patients, a 23.7% decrease from placebo (refer to **Figure 6-11**); but the difference was not statistically significant (p=0.201, log-rank test for time to first definite flare).

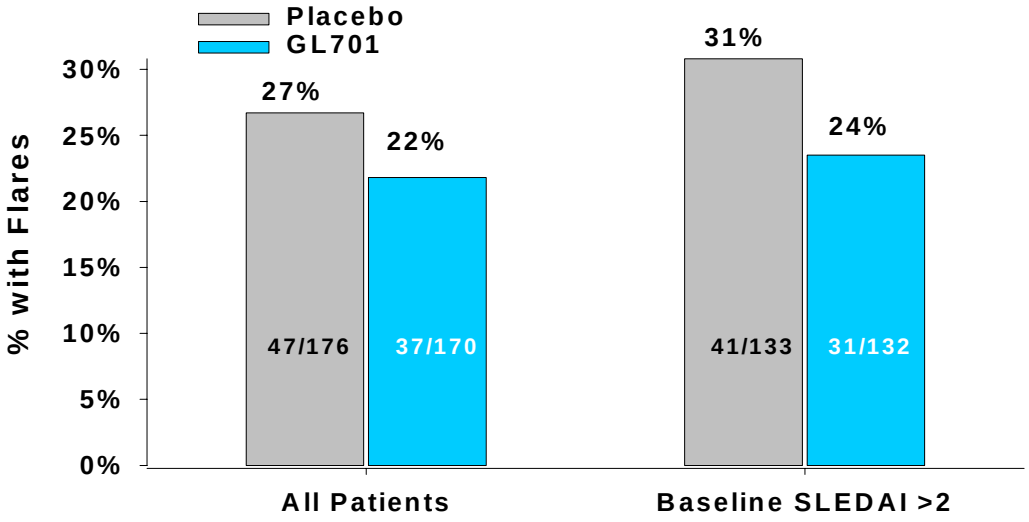


Figure 6-11: Proportion of Patients with Definite Flare

E. Assessment of Bone Density

Eight investigators also conducted bone mineral density (BMD) measurements. At these sites, patients who were on steroids at study entry and for at least the 6 months prior to study entry, had DEXA scans at baseline and at the end of treatment phase. As shown in **Table 6-11** below, the two groups were comparable for important demographic and baseline characteristics, including measures of bone mineral density.

Table 6-11: Selected Baseline Characteristics of Patients Assessed for BMD

Parameter	Placebo N=19	GL701 200 mg N=18
Mean (Median) age	44 (44)	46 (47)
Post-menopausal	9 (47%)	10 (56%)
Estrogen use	6 (31.6%)	3 (16.7%)
Mean (Median) prednisone dose mg/d	6.6 (7.5)	6.1 (5.0)
Immunosuppressive use	5 (26.3%)	5 (27.8%)
Mean (Median) hip T-score	- 0.8 (-1.0)	- 1.0 (- 0.9)

Parameter	Placebo N=19	GL701 200 mg N=18
Mean (Median) L-Spine T-score	- 0.8 (-1.1)	- 1.1 (- 1.0)

In these patients receiving chronic corticosteroid treatment, by 12 months of study, there was a significant decrease in bone density in the placebo group. By contrast, bone density increased in the GL701 group. As shown in **Figure 6-12** below, the differences between GL701 and placebo were seen most prominently in the spine, where the mean decrease of 1.78% in bone density in the placebo group is compared to a mean increase of 1.83% in the GL701 group (p = 0.004). The increase in bone density in the hip with GL701 was similar in magnitude to the effect seen in the spine, though the difference between placebo and GL701 in the hip was not statistically significant from placebo (p = 0.080), in part because there was less decrease in density in the hip than in the spine for the placebo group.

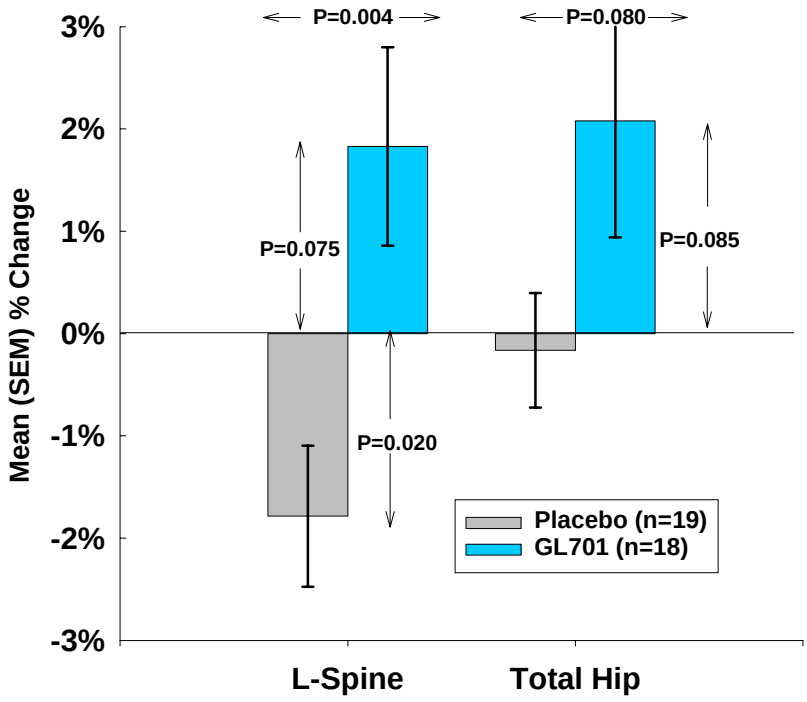


Figure 6-12: Percent change in Bone Mineral Density at 12 Months

6.2.11 Study 95-02 Conclusion

With respect to the objective of the study, improving SLE signs and/or symptoms, the GL701 group had approximately a 35% increase in the proportion of responders, and a 24% decrease in proportion of patients with definite flares. A responder in this study was defined as a patient whose disease activity was stable or improved over the one year duration of study. Analysis of the individual components of the responder definition demonstrated that not one of the 4 scoring instruments dominated the analysis, and that those patients who were non-responders generally had worsening in 1 or 2 of the instruments. Therefore, the treatment effect resulted from the impact of all 4 scoring instruments, with the placebo patients having a higher rate of worsening on any one of the instruments. This suggests that the GL701 treatment effect was relatively broad, showing benefit in constitutional symptoms as well as various manifestations of disease activity. A general trend in favor of GL701 is seen for each of the four instruments used in the responder definition, with Patient VAS approaching statistical significance.

Treatment effects were greatest in patients with baseline SLEDAI > 2 for a number of different variables: responder, flare, and mean changes in SLE scoring instruments. A significant treatment by disease activity (as measured by baseline SLEDAI > 2 yes/no) was found, confirming the hypothesis from Study GL94-01 that patients with low SLEDAI scores responded differently than those with more active disease, indicating that they had less active disease.

6.3 WELL CONTROLLED STUDIES, FOREIGN SOURCE (NON-US IND)

6.3.1 Study GBL96-01 (Disease improvement in SLE – Taiwan Study)

This non-US IND study was conducted by a Genelabs licensee in Taiwan (Genelabs Biotechnologies Co., Ltd.). The study drug was designated by the licensee as “GL701”, though it differed slightly from the Genelabs GL701. The active substance, prasterone, was identical to Genelabs’ GL701: the formulation differed in the amount of one of the excipients. The primary efficacy objective of the study was to demonstrate improvement in women with active SLE. The treatment phase was 6 months. Study GBL96-01 provides foreign source of supportive data from a double-blind placebo-controlled trial, and was conducted in accordance with Good Clinical Practice guidelines.

6.3.1.1 Study Design

GBL96-01 was a multicenter, randomized, parallel group, double-blind, placebo-controlled study. Patients were randomized to receive 200 mg/day GL701 or placebo for 6 months. The study population

was restricted to women with mild to moderately active SLE, defined as patients receiving no prednisone or up to 10 mg/day (or its equivalent of other corticosteroids).

The study was composed of two periods: A Screening/Qualifying period and a double-blind placebo-controlled treatment period. The Screening/Qualifying period was a 7- to 10-day period in which patients had SLAM and SLEDAI measurements taken. SLAM determinations at both baseline visits had to be ≥ 7 (excluding points assessed for ESR). Additionally, SLEDAI determination qualifying visit had to be > 2. The mean of both measurements was used as the baseline value.

6.3.1.2 Population for Analysis

The primary patient population for efficacy analysis was the intent-to-treat population defined in this study as all randomized patients with at least one post-baseline visit.

6.3.1.3 Primary and Secondary Efficacy Variables

A. Primary Endpoint

The primary endpoint was mean change from baseline in the SLAM at 24 weeks of therapy.

B. Secondary Endpoints

Secondary endpoints were similar to those in Study GL95-02 and included:

- Definite flare, defined identically to definite flare in GL95-02,
- Change in SLEDAI , Physician VAS, or Patient VAS score after 6 months

6.3.2 Results

6.3.2.1 Patient Population and Demography

The two treatment groups were well balanced for important demographic and baseline characteristics (**Tables 6-12, 6-13**). There were no significant differences between treatment groups among these variables.

This patient population had some meaningful differences from the population in Study GL95-02. In addition to the difference in race, the patient population in GBL96-02 was younger with a much higher proportion of pre-menopausal patients, approximately 84% compared to 54% in GL95-02. Approximately 97% were receiving corticosteroids compared to 54% in GL95-02. Additionally, 97% had a SLEDAI score > 2 at study entry compared to 77% in GL95-02.

Table 6–12: Baseline Demographics (GBL96-01)

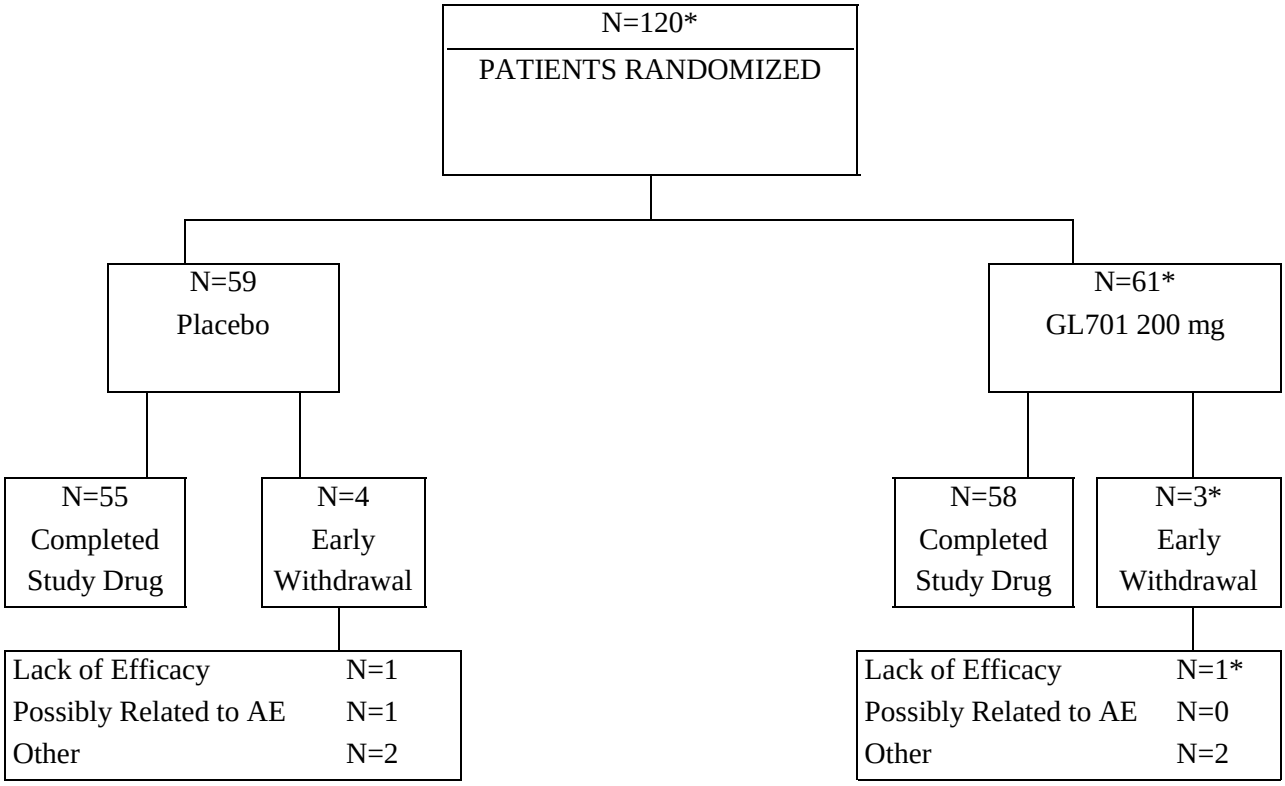
	Placebo N= 59	**GL701 N= 60**
Mean (Median) Age (yrs)	32 (32)	33 (32)
Pre-menopausal	49 (83%)	51 (85%)
Post-menopausal	10 (17%)	9 (15%)

Table 6–13: Baseline Characteristics (GBL96-01)

	Placebo N= 59	**GL701 N= 60**
Mean (Median) Prednisone Dose mg/d	6.7 (5.0)	7.0 (7.5)
Cytotoxic Use (%)	24 (40.7%)	24 (40.0%)
Prednisone Use (%)	58 (98.3%)	58 (96.7%)
Antimalarial Use (%)	41 (69.5%)	39 (65.0%)
SLAM Mean (Median)	10.4 (10.0)	10.3 (9.5)
SLEDAI Mean (Median)	6.6 (6.0)	8.2 (8.0)
Patient VAS Mean (Median)	33.7 (32.5)	37.0 (35.5)
Physician VAS Mean (Median)	31.4 (28.0)	31.0 (30.5)

6.3.2.2 Patient Disposition

Early terminations were similar in the two treatment groups. In the placebo group, 4 of 59 patients (6.8%), as compared with the GL701 group, 3 out of 61 patients (4.9%), withdrew early. **Figure 6-13** below provides a summary of the patients who completed and withdrew from the study as assigned by the investigator. The proportion of patients withdrawing early is less than seen in the US studies, but this may reflect, in part, the shorter duration of planned treatment.



* One patient excluded from ITT because of no post-baseline visits.

Figure 6-13: Disposition of Patients (GBL96-01)

6.3.3 Efficacy Results

6.3.3.1 Primary Efficacy Endpoint - Improvement in SLAM Score

The SLAM score showed within-treatment decreases at last visit within both GL701 and placebo groups. Mean and median values were lower at each post-baseline visit compared to the previous visit in both treatment groups. The GL701 group demonstrated a greater reduction from baseline in both mean and median scores, 2.6 and 2.5, respectively, as compared to 2.0 and 2.0 for the placebo group, but this difference was not significant (p =0.3551).

6.3.3.2 Additional Efficacy Variables

A. SLE Flares

The GL701 group had fewer patients with at least one definite flare. The number of patients with definite flares in the GL701 group was decreased 46.0% compared to placebo (18.3% vs. 33.9%, p = 0.044 based on survival analysis using Cox model). **Figure 6-14** displays the survival curve for time to first definite flare.

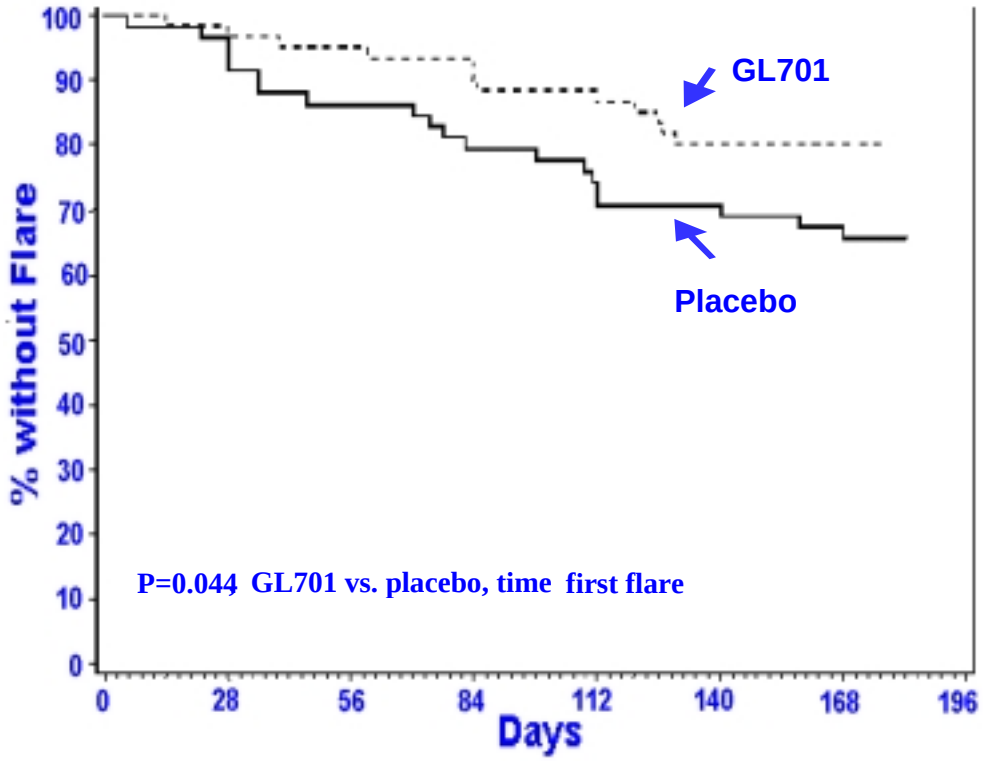


Figure 6-14: Time to First Definite Flare Survival Curve (GBL96-01)

The curves showing the percent of patients without a definite flare begin to diverge at approximately about 28 days of treatment. The difference between treatment groups widens progressively over the entire study. There were no additional patients with definite flares in the GL701 group after 140 days of treatment, whereas new patients with definite flares appear to continue in the placebo group to the end of the study.

B. Improvement in SLAM, SLEDAI, Physician VAS and Patient VAS Scores

The GL701 group showed greater mean and median improvement, compared to the placebo group, for the Patient VAS, Physician VAS, and percent change in SLAM, although only the difference in mean change in Patient VAS was statistically significant (p=0.005). The SLEDAI score showed a greater improvement in the GL701 group median, but not the mean. These results are summarized below in **Table 6-14**.

Table 6–14: Mean Changes in Scoring Instruments at Last Visit

	Placebo N= 59**	**GL701 200 mg N= 60**
SLEDAI Mean (Median)	-1.4 (-0.5)	-1.2 (-1.5)
Patient VAS Mean (Median)	5.4 (0.5)	-5.5 (-6.3)*
Physician VAS Mean (Median)	-6.3 (-7.0)	-9.2 (-7.3)
Percent change in SLAM Mean (Median)	-17.5% (-20.0%)	-24.2% (-28.3%)

*p=0.0046, GL701 200 mg vs. placebo
**Patient count (N) is 58 for SLEDAI Score Placebo group

6.3.3.3 Study GBL96-01 Conclusion

The primary efficacy variable was mean change from baseline to last visit in the SLAM score. Analysis of change from baseline showed that the GL701 group had a greater improvement than the placebo group, although not statistically significant. The overall results of the primary and secondary efficacy analyses, however, consistently showed benefit for GL701 over placebo.

In GL701-treated patients, there was a statistically significant and substantial decrease in the number of patients who experienced at least one flare as compared to the placebo group. This decrease in flares, even greater than the decrease noted in GL95-02, occurred despite study duration of only 6 months compared to one year in GL95-02, possibility reflecting a patient population with more active SLE.

As in Study GL95-02, for the SLE scoring instruments, the pattern was that of improvement (reduction) from baseline to last visit for both treatment groups, but a greater improvement for GL701 than placebo. The greatest difference between treatment groups was in the Patient VAS, where the patients' overall assessment of their disease activity (at the last visit) was one of improvement in the GL701 group, but worsened in the placebo group. This result is similar to the findings of Study GL95-02 as well as the earlier studies of van Vollenhoven (1995).

The findings of the Taiwan study, a non-US IND study conducted by a licensee, support the improvement in SLE noted in Study GL95-02, despite differences in racial makeup of the patient population and potential differences in treatment of SLE between US and Taiwanese physicians. The Taiwanese study enrolled primarily patients (approximately 97%) who were on corticosteroids and had baseline SLEDAI scores > 2, suggesting that the patient population had, on the whole, greater severity or activity of SLE at baseline. Although there were differences in study design including duration of study and definitions of efficacy variables, the Taiwan study, similar to Study GL95-02, demonstrated that GL701 reduced flares

and improved patients' overall assessment (Patient VAS) as compared to placebo. As in Study GL95-02, a general trend in favor of GL701 is seen for scoring instruments used in this study.

6.4 PUBLISHED STUDIES INVESTIGATING DHEA IN SLE (STANFORD UNIVERSITY STUDIES)

DHEA was first studied as therapy for SLE in a small, open-label pilot study, with initial preliminary results published on the first 10 patients (van Vollehoven, 1994). Although only 10 women with SLE, treated 3 to 6 months with DHEA 200 mg once daily, were included in the report, the results were promising with decreases in corticosteroid requirements, SLEDAI score and urinary proteinuria noted. Longer term, open-label efficacy data in 50 women, including the 10 previously studied, were then reported by the same group (van Vollenhoven, 1998). These patients also received DHEA 200 mg once daily, but were allowed to decrease the dose to 100 mg or 50 mg if there was poor tolerance. In these patients, treated up to 12 months, significant decreases from baseline were noted for SLEDAI, patient VAS, and physician VAS, prednisone dose was also significantly decreased. This treatment effect increased incrementally over the 12 months. However, since approximately 30% of the patients terminated early due to lack of efficacy, 32% of the patients by 6 months and 58% by 12 months, "survivor bias" may have influenced these positive results.

A small placebo-controlled trial provided additional evidence of efficacy (van Vollenhoven, 1995). In the initial double-blind phase of this study, 28 women with mild to moderate SLE received 200 mg DHEA or placebo once daily for three months. In this small randomized study, there were some baseline imbalances: baseline SLEDAI and prednisone dose were higher in the DHEA group. Overall, the DHEA group showed decreases in SLEDAI, physician VAS, and patient VAS scores; and prednisone dose decreased, while in the placebo group these scores either increased or remained unchanged and prednisone dose increased. The difference between treatment groups for patient VAS was significant ($P = 0.022$). In addition, lupus flares were more frequent in the placebo group, occurring in 8 of 14 placebo patients, vs. 3 of 14 DHEA patients ($p = 0.053$). However, no precise or pre-determined definition of flare was used.

DHEA was also investigated in 19 patients with more severe SLE (van Vollenhoven, 1999). Severe lupus was defined as severe renal, hematological or serosal lupus, newly present or present for at least one month despite conventional therapy. There were specific objective findings required for these organ systems. These objective findings were then followed, and the primary analysis of efficacy was a responder analysis based on specific improvement in the organ system involved at baseline. For example, for severe renal lupus, two of following were required: (1) proteinuria of 3 g/day or 2-3 g/day with

clinical manifestations of nephrosis; (2) RBC casts of 20 RBC/hpf; (3) a reduction in creatinine clearance by 30% in the previous 3 months. To be a responder, such a patient had to stabilize renal disease, defined as proteinuria < 2 g/day or less than half of baseline proteinuria, and not have clinical manifestations of nephrosis, and not have RBC casts and < 20 RBC/hpf, and have creatinine clearance decreased < 20% of baseline. The starting dose was 200 mg once daily, but dose reduction to 200 mg every other day was allowed if there was treatment-related adverse experience. Treatment duration was 6 months. Secondary efficacy variables were SLEDAI, SLAM, Patient VAS, and Physician VAS. In addition, changes in bone density were evaluated by DEXA scans.

As in the previous randomized, controlled study, small sample size resulted in baseline imbalances. The most notable differences were higher baseline scores for all four scoring instruments in the DHEA group, with Physician VAS being significantly different. In addition, all four patients with serositis were randomized to placebo. The responder rate was 7of 9 in the DHEA group vs. 4 of 10 in the placebo group ($P < 0.10$). All 4 patients with serositis were non-responders. Mean SLEDAI scores showed a greater decrease in the DHEA group ($p = 0.07$), but since the SLEDAI score is highly influenced by renal components, and less by serositis, regression to the mean in the greater proportion DHEA patients with renal disease would lead to apparent larger mean decreases in SLEDAI. Thus, the investigators concluded that there may have been a small benefit from DHEA in serious SLE, but the small patient numbers limited generalizabilty of the results of this study.

The relationship of dose of DHEA to serum levels, efficacy and side effects was investigated in a small study (van Vollenhoven, 1998). In this study, women with SLE were initially treated with 50 mg/day of DHEA, which was increased stepwise monthly to 600 mg/day if neither side effects nor “remission” was achieved. Remission was defined as a SLAM < 4. Twenty-two patients achieved a maximum dose under this algorithm by 6 months. A maximum dose of only 100 mg/day in 4 patients, and 200 mg/day in an additional 4 patients was achieved. Dose escalation in these 8 patients was stopped due to side effects, mainly acne in 6 and “remission” in 2. In the 14 patients who had not achieved a maximum benefit or limiting side effects the dose was increased. Escalation was stopped at 400 mg/day in 11 of these, 6 due to side effects and 5 due to “remission.” The remaining 3 patients met the criteria of remission at 600 mg/day.

There was a linear relationship between dose and peak serum levels of DHEA and DHEA-S, with, however, considerable variation in levels among patients at any dose. For example, peak serum levels of DHEA ranged from approximately 350 to 3500 ug/dl at a dose of 400 mg/day. The investigators attempted to determine a relationship between serum levels of DHEA or DHEA-S and clinical

improvement. Using an assumption of second order linear regression (i.e., that there might be an "optimum" serum level with decreasing efficacy above that serum level), they found a trend toward increasing efficacy, as defined by "remission" and higher serum levels. Serum levels of DHEA, DHEA-S or testosterone did not correlate with the occurrence of acne.

Any conclusions from this study are limited by its small size. However, the investigators concluded that there was poor correlation of oral dose of DHEA to efficacy or serum levels of DHEA or DHEA-S. Thus, there was no dose response relationship. There was weak correlation of serum levels with efficacy, but not enough to justify monitoring of serum levels. They suggested that individualizing dose would be the most prudent approach.

In summary, in a series of small, single institution clinical studies, investigators at Stanford University have provided evidence that DHEA, at least at 200 mg/day, improves disease activity in SLE and allows reduction of corticosteroid dose. These studies, although limited by small patient numbers, provided impetus for the Genelabs Phase III studies, but also provide independent support for the results of the Phase III studies.

6.5 DISCUSSION OF EFFICACY

6.5.1 Population Subsets

6.5.1.1 Pre- and Post-Menopausal Patients

Menopausal status did not appear consistently to influence responder status in all randomized patients or patients with active disease (baseline SLEDAI > 2). Results for baseline SLEDAI > 2 are presented in **Table 6-15**.

Table 6–15: Responder[1] Rate by Menopausal Status

Study	Baseline SLEDAI > 2	
Treatment	**Pre-Menopausal**	**Post-Menopausal**
GL94-01		
Placebo	8/28 (28.6%)	5/17 (29.4%)
GL701 100 mg	11/32 (34.4%)	7/15 (46.7%)
GL701 200 mg	17/35 (48.6%)	6/10 (60.0%)
GL95-02		
Placebo	39/70 (55.7%)	26/63 (41.3%)
GL701 200 mg	50/75 (66.7%)	37/57 (64.9%)

[1]Responder defined in GL94-01as sustained reduction to physiological levels of prednisone while keeping disease activity constant or improved; and defined in GL95-02 as improvement or stabilization of disease while keeping prednisone dose constant.

6.5.1.2 Race

The responder rates did not appear to vary meaningfully by race in all randomized patients or patients with baseline SLEDAI > 2. Results for baseline SLEDAI > 2 are presented in **Table 6-16** below.

Table 6-16: Responder[1] Rate by Race

Study	Baseline SLEDAI > 2		
Treatment	**Caucasian**	**African-American**	**Other**
GL94-01			
Placebo	11/31 (35.5%)	2/12 (16.7%)	0/2 (0%)
GL701 100 mg	12/26 (46.2%)	4/12 (33.3%)	2/9 (22.2%)
GL701 200 mg	11/23 (47.8%)	5/11 (45.5%)	7/11 (63.6%)
GL95-02			
Placebo	47/90 (52.2%)	7/25 (28.0%)	11/18 (61.1%)
GL701 200 mg	68/100 (68.0%)	11/17 (64.7%)	8/15 (53.3%)

[1]Responder defined in GL94-01as sustained reduction to physiological levels of prednisone while keeping disease activity constant or improved; and defined in GL95-02 as improvement or stabilization of disease while keeping prednisone dose constant.

6.5.1.3 Patients with Greater SLE Disease Activity

Patients entering the placebo-controlled studies had mild to moderate, active SLE. In Study GL94-01, this was defined as steroid dependent and receiving 10 to 30 mg/day prednisone or its equivalent. In GL95-02 and the Taiwan study, it was initially defined as SLAM $\geq$ 7, and receiving up to 10 mg/day prednisone or its equivalent; and later amended to also require SLEDAI > 2.

Although the patients were characterized as having mild to moderate SLE, a significant proportion of patients had moderately severe SLE as characterized by baseline SLEDAI. For example, in GL94-01, 50% of all patients had a SLEDAI score > 4, and 22% a SLEDAI score > 8. In GL95-02, 59% of all patients had a SLEDAI score > 4, and 24% a SLEDAI score > 8.

As part of the NDA review, FDA requested that the efficacy variables for both studies be stratified by categorical baseline SLEDAI scores. This analysis, in both GL94-01 and GL95-02, demonstrates that the difference in responder rates between placebo and GL701 increased with increasing severity of SLE, at least as measured by baseline SLEDAI.

In GL94-01, as can be seen from **Figure 6-15** presented below, all three treatment groups exhibited similar proportions of responders for patients with baseline SLEDAI $\leq$ 2. With greater severity of disease at baseline, however, it is evident that the proportions of responders in the placebo group decline rapidly with increasing baseline SLEDAI scores while the proportion of responders in the GL701 200 mg group was relatively maintained for each categorical baseline SLEDAI score, resulting in a progressively greater difference between placebo and GL701 200 mg with greater baseline disease severity (as measured by SLEDAI).

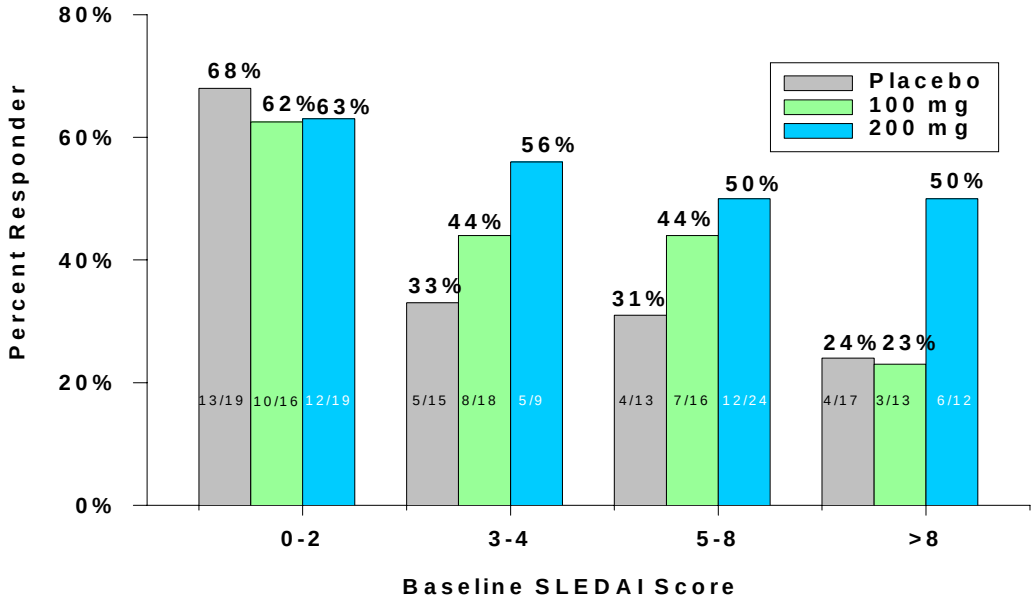


Figure 6–15: GL94-01 Responders

In GL95-02, when severity or activity of SLE is categorized by baseline SLEDAI score categories, and proportion responders are stratified by these categories, there again appears to be an increasing difference between the GL701 and placebo groups with increasing SLE activity as determined by baseline SLEDAI score (**Figure 6-16**).

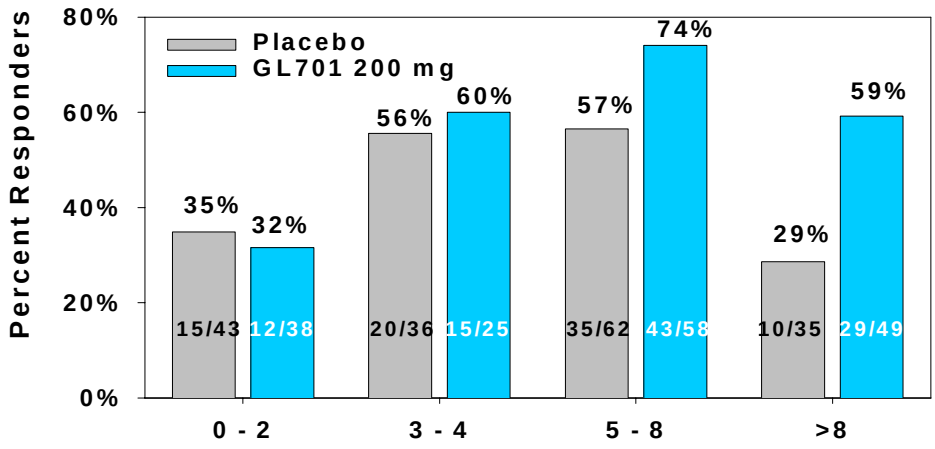


Figure 6–16: Responders by Baseline SLEDAI Score (Study GL95-02)

This finding, a greater difference in efficacy as baseline SLEDAI score increases, appears to be true for flares, though with the smaller number of flares, this relationship is not consistent for each SLEDAI category (refer to **Figure 6-17**).

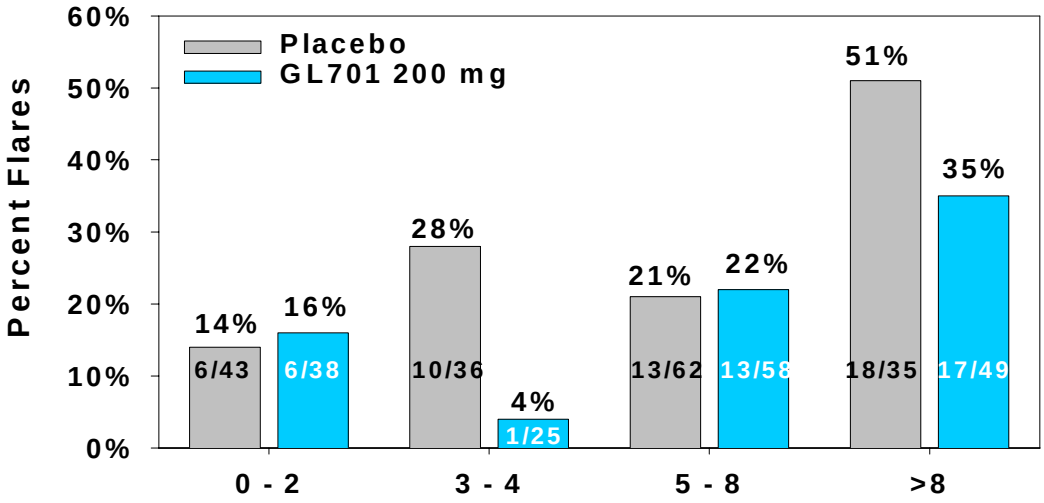


Figure 6–17: Flares by Baseline SLEDAI Score (Study GL95-02)

Consistent with the findings described above for patients receiving corticosteroids in Study GL95-02, these results suggest that, within the spectrum of patients with active SLE entered to these studies, i.e., patients without severe organ damage, GL701 demonstrates as good as, if not better, treatment effect in those patients with more severe SLE than in those with less severe disease.

6.5.1.4 Concomitant Antimalarials

In both studies, concomitant hydroxychloroquine and other antimalarials were allowed, and the protocol required that they be kept constant during the study, except for changes in dose required by toxicity. In GL94-01, approximately 49% of the study population were receiving antimalarials at study entry; and in GL95-02, approximately 25% of the per-protocol population were using antimalarials.

As shown in **Table 6-17** below, in both double-blind studies, for active treatment (GL701 100 mg and 200 mg) the responder rate was higher in patients receiving antimalarials at study entry, in comparison to those not on antimalarials. For the placebo groups, in the steroid sparing study, GL94-01, the response rate was lower in those on antimalarials in comparison to placebo patients not receiving antimalarials, while in GL95-02, this relationship was reversed. Placebo patients on antimalarials at baseline had a higher response rate than placebo patients not on antimalarials. Thus, in both studies, patients randomized to GL701 and receiving antimalarials at study entry had a higher response rate than those not receiving antimalarials, and in GL94-01, additionally, the difference between GL701 and placebo was greater in patients receiving antimalarials.

These data are consistent with the possibility that GL701 and antimalarials, given together, have greater effect. However, since in neither study were the groups randomized or stratified for antimalarial use, any such conclusion is highly speculative. The data are also consistent with the possibility that antimalarial use was a proxy for more severe or active SLE, which explain why there might have been a greater difference between placebo and GL701 in Study GL94-01.

Table 6-17: Responder[1] Rate by Antimalarial use

Study	No Antimalarial Use at Baseline			Antimalarial Use at Baseline		
Patient Group	**Placebo**	**GL701 100 mg**	**GL701 200 mg**	**Placebo**	**GL701 100 mg**	**GL701 200 mg**
GL94-01						
Baseline SLEDAI > 2	10/24 (41.7%)	8/32 (25.0%)	10/23 (43.5%)	3/21 (14.3%)	10/15 (66.7%)	13/22 (59.1%)
GL95-02						
Baseline SLEDAI >2	45/99 (45.5%)		68/106 (64.2%)	20/34 (58.8%)		19/26 (73.1%)

[1]Responder defined in GL94-01as sustained reduction to physiological levels of prednisone while keeping disease activity constant or improved; and defined in GL95-02 as improvement or stabilization of disease while keeping prednisone dose constant.

6.5.1.5 Concomitant Corticosteroids

In Study GL94-01 and the Taiwan study, close to 100% of patients were receiving corticosteroids.

However, for Study GL95-02, the entry criteria required that patients be on a stable prednisone dose (or prednisone equivalent) of 10 mg/day or less. Approximately 45% of the patients were not receiving corticosteroids at study entry. As shown in **Table 6-18**, in GL95-02, both for responders and for flares, the greatest difference between placebo and GL701 was noted in patients receiving corticosteroids at study entry. This difference appears to be due to a lower response rate and a higher flare rate, especially in the placebo group, in those patients who were receiving corticosteroids at study entry. Since the patients continued their corticosteroids on study, this suggests that the patients already receiving corticosteroids had more severe or more active SLE.

Examination of DHEA-S levels at study entry demonstrates that the patients requiring corticosteroids tended to have lower levels of DHEA-S. DHEA-S levels at study entry were 51.2µg/dl for placebo and 64.5 µg/dl for GL701 patients on corticosteroids at study entry compared to 168.8µg/dl and 160.7µg/dl for placebo and GL701 patients not on corticosteroids. Lower DHEA-S levels in patients receiving corticosteroids could be explained by corticosteroid suppression of endogenous DHEA-S, or by low DHEA-S levels being a sign of greater severity or activity of SLE in patients requiring corticosteroids, or by a combination of these two factors. Either explanation of lower DHEA-S levels in SLE patients in patients receiving corticosteroids would be compatible with the observation of a greater treatment difference between GL701 and placebo in these patients.

As described in **Section 4.3 Pharmacology**, GL701 treatment increased DHEA-S levels to levels far above baseline, even in those patients on corticosteroids who had the lowest baseline DHEA-S levels.

Table 6–18: Responder and Flare Rates by Corticosteroid Use (GL95-02)

Patient Group	Placebo	GL701	P value*
	Percent Responders		
Corticosteroids at study entry	40/98 (40.8%)	52/91 (57.1%)	0.025
No Corticosteroids at study entry	40/78 (51.3%)	47/79 (59.5%)	0.301
	Percent Flares		
Corticosteroids at study entry	36/98 (36.7%)	23/91 (25.3%)	0.089
No Corticosteroids at study entry	11/78 (14.1%)	14/79 (17.7%)	0.535

*P-value is based on chi-square test

6.5.1.6 Dose Response

The choice of dosage used in clinical trials for GL701 was based on the results of Phase II studies at Stanford University in which DHEA 200 mg/day appeared effective and safe in SLE. Both of the Genelabs double-blind, placebo-controlled studies, as well as the open-label extension study, also show that 200 mg/day is effective in decreasing or stabilizing disease activity, or enabling reduction of

corticosteroid dose. This dose is well tolerated, but does cause an increase in mild androgenic adverse events, especially acne and hirsutism, in some patients that may lead to premature termination of treatment.

In GL95-02, where the objective was improvement in SLE disease activity, only one dose, 200 mg/day, was investigated. However, in the first Phase III study, GL94-01, where the objective was steroid sparing, 100 mg/day and 200 mg/day were compared to placebo. In GL94-01, in patients with baseline SLEDAI > 2, where a treatment effect was most marked, the proportion of responders (patients achieving sustained reduction of corticosteroid dose), receiving 200 mg/day GL701 was significantly higher than placebo (51.1% vs. 28.9%, $p = 0.031$). The response rate for 100 mg/day, 38.3%, was intermediate, between placebo and 200 mg/day, but not significant ($p = 0.339$ for comparison with placebo). However, a linear trend test suggests a dose response relationship ($p = 0.033$) for patients with baseline SLEDAI >2.

Similarly, for other measures of steroid sparing, such as proportion of patients achieving physiological doses of prednisone ($\leq$ 7.5 mg/day) at each monthly visit, or total number of days prednisone dose was $\leq$ 7.5 mg/day, the GL701 100 mg/day dose showed an improvement compared to placebo, but a smaller improvement than the 200 mg/day dose.

Increased production of testosterone might be considered a pharmacodynamic effect of GL701 administration. Testosterone serum levels in GL94-01 also showed a dose response relationship. For testosterone, the mean changes in serum levels from baseline in the placebo, 100 mg and 200 mg groups were 0.5, 22.2, and 56.9 ng/dl, respectively. Similarly, as described above in **Section 4.3 Pharmacology**, serum levels of DHEA-S increased with increasing dose. However, as shown also by van Vollenhoven et al. (1998) there was considerable variability in mean levels with a SD of approximately 100% of serum levels for placebo and both 100 mg and 200 mg doses, and a wide range for individual patients. For example, in the placebo group, the values at the last visit ranged from 0 to 206 μg/dl, thus showing the wide variability in endogenous DHEA-S levels; and in the 200 mg dose group, the range was 9 to 3827 μg/dl.

Thus, the Stanford University "dose finding study" (Barry, 1998) and Studies GL94-01 and GL95-01 provide some evidence that some patients respond to 100 mg/day, but many more patients benefit at 200 mg/day. The Stanford University study also suggests that some patients might require even higher doses. These studies also suggest that in patients with SLE there appears to be wide variability in serum levels of DHEA or DHEA-S.

6.5.1.7 Integrity of the Treatment Blind

In both studies, all study medications were identical in appearance (opaque, white, gelatin capsules). In order to prevent possible unblinding by results of serum DHEA-S or hormone level results, these results were not supplied to the investigator until the study was complete and the database locked. All decisions regarding patient data handling were made prior to unblinding.

Unblinding of individual patients by efficacy or certain adverse events is potentially possible in any double-blind study. However, SLE is a multi-systemic disease that characteristically waxes and wanes, making it difficult to attribute changes in individual patients to active treatment. There were no reports from investigators of any specific pattern of efficacy results allowing them to guess treatment code.

With regard to potential unblinding by adverse events, patients or physicians may have tried to guess the treatment code on the basis of known or anticipated androgenic adverse effects, such as hirsutism or acne or seborrhea. However, it would have been very difficult for unblinding to have occurred in any systematic way since these events, probably also increased by concomitant corticosteroids, also occurred in placebo patients. For example, as described subsequently in **Section 7.2.**, acne was the most common adverse event, occurring in approximately 44% of GL701 patients in GL94-01 and 33% of GL701 patients in GL95-02, but it also occurred in approximately 19% and 14% of placebo patients in both studies respectively. Hirsutism was reported by approximately 12% of GL701 patients in GL94-01 and 16% of GL701 patients in GL95-02, but was also reported by approximately 5% and 2% of placebo patients in both studies respectively. In GL95-02, 42% (72 of 170) per-protocol GL701 patients reported acne, hirsutism, or both events, compared to 18% (31 of 176) placebo patients. Thus, although an individual patient with acne or hirsutism guessing solely on the basis of these adverse events that she was on GL701 would be twice as likely to be correct than by chance, a substantial number of placebo patients would be guessing incorrectly.

Nevertheless, the possible impact of these adverse events on the efficacy results of Study GL95-02 was analyzed. In the placebo group, the proportion of responders in those patients who reported acne and/or hirsutism was 35% (11 of 31) compared to 48% (69 of 145) placebo patients without these androgenic events. (**Table 6-19**) Similarly, for the Patient VAS, arguably the most subjective variable, there was greater improvement in patients without acne or hirsutism. The mean change for placebo patients experiencing acne or hirsutism was –3.7, compared to –4.5 for those without these events. The lack of correlation of androgenic events with increased efficacy in placebo patients suggests that simply the occurrence of these androgenic events by themselves did not predispose patients or investigators towards reporting greater efficacy.

In patients receiving GL701, those experiencing acne and/or hirsutism had a higher response rate compared to GL701 patients without these events: 68% (49 of 72) of those patients with androgenic events were responders compared to 51% (50 of 98) without androgenic events (**Table 6-19**). Similar findings are noted with improvement in the patient VAS, where there was greater improvement in those GL701 patients with androgenic events compared to those not have such events. However, unlike this analysis of the placebo group, such an analysis of those on active treatment is confounded by the fact that the occurrence of androgenic adverse events correlates with the desired pharmacodynamic effect: increasing androgenic effects. The rationale of the use of GL701 in SLE is the observed decreased levels of androgens including DHEA in SLE, and the finding that androgen treatment, including DHEA, improves SLE in murine models. In placebo patients, there would be no such confounding, and placebo patients did not appear to be influenced by androgenic events to report greater efficacy.

Table 6–19: Androgenic Aes and Responders

Placebo	N	Percent Responders	Mean Change Patient VAS	GL701	N	Percent Responders	Mean Change Patient VAS
Androgenic AE	31	11 (35.5%)	-3.7	Androgenic AE	72	49 (68.1%)	-9.0*
No Androgenic AE	145	69 (47.6%)	-4.5	No Androgenic AE	98	50 (51.0%)	-4.2

*N = 71 for Patient VAS

6.5.1.8 Clinical Relevance of Endpoints

The primary efficacy variables used in GL94-01 and GL95-02 are new, as they were developed as a collaborative process for these two studies. Nevertheless, each appears relevant for patients with SLE.

In GL94-01 the endpoint, responder, was based on sustained prednisone reduction while maintaining constant or improved disease activity. For the purposes of the protocol, this endpoint was precisely defined, as reduction of prednisone or its equivalent to $\leq$ 7.5 mg/day sustained for at least the last two months of the study. A responder by this definition would appear to have had a clinically meaningful result: a decrease in prednisone requirements to doses at or below replacement levels. Achieving this level of prednisone reduction is generally regarded by both the patient and physician as an important goal, in patients who would otherwise be at risk of prednisone-related complications. Other measures of prednisone reduction, such as the number of days at 7.5 mg or lower, and proportion of patients with prednisone dose at this level at each visit also suggested a benefit for GL701, a benefit that seems equally clinically important.

In GL95-02, the primary endpoint, responder, was also a per-patient endpoint developed for that study. A responder in this study was defined as a patient whose disease activity was stable or improved over the one year duration of study. This definition integrated the three recognized domains in SLE: measures of physician assessed disease activity, the SLEDAI and SLAM scores, and measures of patient assessed disease activity, the KFSS and Patient VAS. In addition, to be a responder the patient could not have had clinical deterioration, which was defined as significant organ damage, toxicity, or increase in SLE medications. This integration was accomplished by requiring that the mean of all on-treatment scores be unchanged or improved compared to the mean of the baseline scores for each of the four scores. Since the responder definition integrated the results at all four visits for each of the four scores, it identifies patients whose SLE, as judged by both patient and physician, overall remained stable or improved over a year.

In GL95-02, the clinical relevance of an increased percentage of responders in the GL701 group is shown by the fact that this increase in responders was accompanied by a similar decreased percentage of patients with flares, decreased percentage of patients reporting mucosal ulcers, myalgias and alopecia, as well an improvement in the patient's own global assessment of disease.

6.5.2 Overview of Efficacy of GL701 in SLE

The efficacy of GL701 in women with SLE was demonstrated in two US placebo-controlled, double-blind randomized clinical trials. In the first study, GL94-01, the objective was to determine whether GL701 would allow steroid-dependent (daily prednisone dose 10 to 30 mg) patients to reduce their corticosteroid requirements while improving or maintaining disease activity. In the second study, GL95-02, the objective was to determine whether GL701 could improve disease activity in patients active SLE, while remaining on a stable background of SLE medications (daily prednisone dose 0 to 10 mg).

Because of the requirement of a lower corticosteroid dose at study entry, it might appear that patients in GL95-02 would have entered the study with milder disease than patients in GL94-01. However, review of the baseline and demographic characteristics of the patient populations used for analysis in these two studies suggests that the two study populations were not dissimilar with respect to disease activity, although there were some differences in demographic characteristics (**Table 6-20**). In comparison to GL94-01, GL95-02 patients were slightly older, had a somewhat greater proportion of Caucasians, and had a substantially greater proportion of patients classified as post-menopausal at study entry. Despite their lower prednisone dose at baseline (as required by the protocol), GL95-02 patients in general had slightly more active SLE, as measured by any of the 6 scoring instruments displayed below. In addition,

in GL95-02, approximately 17% of the patients were receiving immunosuppressives, while in GL94-01, patients requiring immunosuppressives were excluded.

Table 6–20: Demographic and Baseline Characteristics

	Study GL94-01 N = 191*	**Study GL95-02 N = 346****
Mean Age	40.3	43.9
Caucasian	60.2%	74.3%
Post-Menopausal	28.3%	46.2%
Mean (Median) Prednisone Dose	14.2 (12.5)	3.6 (3.0)
Prednisone Use	100%	54.6%
Immunosuppressive Use	0	16.2%
Antimalarial Use	48.7%	25.1%
Mean DHEA-S levels at baseline	48.6 ug/dl	104.2 ug/dl
SLEDAI Score (Mean)	5.9	6.2
Patients with baseline SLEDAI > 2	71.7%	76.6%
Patient VAS (Mean)	47.4	55.2
Physician VAS (Mean)	25.8	30.5
Krupp Fatigue Score (Mean)	5.2	5.5
SF-36 Mental Component (MCS) (Mean)	44.4	42.2
SF-36 Physical Component (PCS) (Mean)	33.2	31.4

*All patients
**Per-protocol patients

The response rates in the two studies are summarized in **Table 6-21.** Although the definitions of response in the two studies were very different, nevertheless, the percent improvement in response in the GL701 group over the placebo group is greater in both Studies GL94-01 and GL95-02.

Table 6–21: Percent Responders[1]

Study	Group	Placebo	GL701 100 mg	GL701 200 mg
GL94-01[1]	All Patients	26/64 (40.6%)	28/63 (44.4%)	35/64 (54.7%)
	P-value		P=0.663	P=0.111
	Percent Improvement vs. Placebo		9.3%	34.7%
	Baseline SLEDAI > 2	13/45 (28.9%)	18/47 (38.3%)	23/45 (51.1%)
	P-value		P=0.339	P=0.031
	Percent Improvement vs. Placebo		32.5%	76.8%
GL95-02[1]	All Patients	80/176 (45.5%)		99/170 (58.2%)
	P-value			P=0.018
	Percent Improvement vs. Placebo			27.9%
	Baseline SLEDAI > 2	65/133 (48.9%)		87/132 (65.9%)
	P-value			P=0.005
	Percent Improvement vs. Placebo			34.8%

[1]A responder in GL94-01 was a patient who achieved sustained (at least 2 months) corticosteroid reduction to $\leq$ 7.5 mg/day prednisone; a responder in GL95-02 was a patient whose SLEDAI, SLAM, KFSS and Patient VAS scores improved or stabilized over the study, and who had no clinical deterioration.

Study GL94-01 demonstrated that more patients receiving GL701 were able to achieve sustained reduction of prednisone dose to physiological levels, as defined in the protocol. However, because of the forced titration design required by the endpoint of steroid reduction, other efficacy variables could not be expected to show improvement, since as a patient;s disease improved or remained stable, her prednisone dose would be reduced. Thus, the findings in GL94-01 are somewhat more limited than in GL95-02. It had smaller patient numbers, and the results achieved $P < 0.05$ only for patients with baseline SLEDAI > 2. Nevertheless, the findings of GL94-01, that GL701 enabled patients to reduce their corticosteroid without increase in disease activity, are consistent with previous findings at Stanford University (van Vollenhoven, 1995).

In Study GL95-02, the sample size was larger than in GL94-01 and the two treatment groups were well balanced for all important demographic and baseline values. In addition to a significantly greater

improvement for GL701 in the primary efficacy variable, responder, virtually all of the secondary variables, such as time to flare and mean changes in SLEDAI, SLAM, Patient VAS, and Physician VAS favored GL701, with the greatest difference noted in Patient VAS.

When the results of these two double-blind, placebo-controlled studies are assessed together, evidence supporting the efficacy of GL701 is stronger. In two separate studies, with entirely different endpoints, the GL701 group showed significantly better efficacy in comparison to placebo in patients with active SLE. The studies were relatively large for an orphan drug patient population, with 191 and 381 patients (346 patients in the per-protocol population); patients were followed for 7 to 12 months; and the studies were blinded.

The results from the two phase III trials are consistent with the earlier pilot studies at Stanford University: steroid reduction, decreased flares, improvement in overall disease activity as measured by Patient VAS. More importantly, the results in GL95-02 are confirmed by a subsequent parallel group double-blind placebo-controlled trial in Taiwan, Study GBL96-01, with a study design quite similar to GL95-02. The study populations in both studies were women with mild to moderate active SLE, with active SLE defined as baseline SLAM $\geq$ 7 and later, by amendment SLEDAI score > 2. The Taiwan study was amended early during the trial process, so approximately 97% of the patients met the amended definition of active SLE, compared to approximately 76% in GL95-02. Additionally, efficacy assessments used in the Taiwan study, such as the SLE scoring instruments, SLEDAI, SLAM, Patient VAS and Physician VAS were similar to the ones used in the US studies. Importantly, both studies used identical flare definitions. There were some demographic differences between the US and Taiwan study populations. The Taiwan study population was exclusively Chinese; had a much higher proportion of patients receiving steroids at study entry, approximately 97% compared to approximately 55% in GL95-02; and had a higher proportion of pre-menopausal patients, approximately 80%, compared to 54% pre-menopausal in GL95-02. An important difference between the two studies was that the treatment period in the Taiwan study was 6 months compared to 12 months in GL95-02.

Despite these differences, there is consistency across studies in the efficacy outcome. In both the Taiwan study and GL95-02, flares were substantially reduced in the GL701 group compared to placebo. In the Taiwan study, this difference was statistically significant, while in GL95-02, this difference was in favor of GL701, but not statistically significant. In the pilot study at Stanford University, Patient VAS showed significant improvement in the DHEA group compared to placebo. Similarly, in both the Taiwan study and GL95-02, patients' overall assessment of their disease status, as measured by VAS, showed greater improvement in the GL701 group, compared to placebo. The finding of an overall improvement as

measured by the patient's global assessment was also a significant finding in the Stanford University double-blind, placebo-controlled study (van Vollenhoven, 1995).

7 SAFETY

7.1 ORGANIZATION OF SAFETY ANALYSES

The primary analysis of safety is from the two double-blind, placebo-controlled, parallel design studies, GL95-02, and GL94-01, under US IND, where adverse events rates and clinical laboratory changes can be most meaningfully analyzed in comparison with placebo. Thus the safety data from these two studies have been pooled. Additional placebo-controlled safety data, analyzed separately, comes from the randomized double-blind, parallel design study, GBL96-01, a foreign (Taiwan) study not conducted under a US IND. This study was similar in design to GL95-02, differing mainly by having a shorter duration (six months compared to one year for GL95-02) and different demographics.

Analysis of longer-term safety comes from the open-label extension study, GL95-01. In this study, patients began open-label GL701 treatment after being on placebo in either Study GL94-01 or GL95-02 or continued to receive GL701.

Additionally, GL701 effects on levels of sex steroids are reported from short-term pharmacokinetic studies in normal female subjects. In these studies, data regarding levels of estradiol and testosterone were obtained under more controlled conditions with regard to timing of menses or menopausal status; and there is no confounding use of hormone replacement therapies.

7.1.1 Extent of Exposure

Over 300 women have been treated with GL701 for at least six months, and over 200 for at least one year (**Table 7-1**).

Table 7-1: Duration of Exposure

	Duration of Exposure to GL701[1]			
	Any exposure	**≥ 6 Mos.**	**≥ 12 Mos.**	**≥ 18 Mos.**
Number of female patients[2]/healthy volunteers	**641[3,4]**	**387**	**242**	**138**
Duration of treatment by menopausal status:				
No. Pre-menopausal		229	150	86
No. Post-menopausal		158	92	52

1. GL701 dose of 200 mg/d, except for 63 female SLE patients treated at 100 mg/d in GL94-01 for up to 9 months, and patients who reduced dose during open-label Study GL95-01.
2. 24 male SLE patients in placebo-controlled Study GL97-01 are excluded because their treatment code remains blinded.
3. Includes 87 healthy female volunteers treated at 200 mg/day
4. Includes 61 female SLE patients treated at 200 mg/day in non-US IND study in Taiwan, GBL96-01.

7.1.2 Demographics

Demographic characteristics of GL94-01 and GL95-02 are presented in **Table 7-2** below. Mean age for both studies was approximately 40-44 years and slightly more than half the patients in both studies were pre-menopausal.

Table 7-2: Demographic Characteristics (GL94-01 and GL95-02)

	Placebo N =256	**GL701 100 mg N = 63**	**GL701 200mg N = 253**
Age (yrs)			
Mean	43.0	40.0	43.3
Median	42.0	39.0	43.0
Range	18.0-70.0	18.0-75.0	18.6-69.1
Race			
Caucasian	181 (71%)	36 (57%)	181 (72%)
African-American	50 (20%)	16 (25%)	39 (15%)
Asian	5 (2%)	2 (3%)	3 (1%)
Hispanic	16 (6%)	8 (13%)	24 (10%)
Other	4 (2%)	1 (2%)	6 (2%)
Menopausal Status			
Pre-Menopausal	143 (56%)	42 (67%)	158 (62%)
Post-Menopausal	113 (44%)	21 (33%)	95 (38%)

As described in **Section 6.3.2** the population in the Taiwan study was exclusively Chinese, mainly pre-menopausal (84%) and younger (median age 32), than the population in the US studies.

7.2 ADVERSE EVENTS

7.2.1 All Adverse Events

Table 7-3 displays all adverse events reported in a frequency of 10% or greater from either the 200 mg dose group or the placebo group for the pooled double-blind phases of Studies GL94-01 and GL95-02. Because the number of patients who received GL701 100 mg was substantially fewer, adverse events for this group are only presented for those adverse events which were reported in $\geq$ 10% of either placebo or GL701 200 mg patients. Patients with multiple adverse events of the same nature (e.g., arthritis reported on two or more occasions) are counted only once for this analysis.

Table 7-3: Pooled adverse events with frequency ≥10%*
(GL94-01 and GL95-02)

COSTART TERM	Placebo N=256	GL701 100mg N=63	GL701 200mg N=253
Rash	77 (30.1%)	14 (22.2%)	93 (36.8%)
Acne	39 (15.2%)	28 (44.4%)	91 (36.0%) **
Arthralgia	95 (37.1%)	15 (23.8%)	88 (34.8%)
Asthenia	70 (27.3%)	23 (36.5%)	68 (26.9%)
Headache	76 (29.7%)	17 (27.0%)	60 (23.7%)
Arthritis	58 (22.7%)	17 (27.0%)	57 (22.5%)
Myalgia	79 (30.9%)	14 (22.2%)	55 (21.7%) **
Pain Abdomen	34 (13.3%)	8 (12.7%)	41 (16.2%)
Flu Syndrome	46 (18.0%)	1 (1.6%)	40 (15.8%)
Stomatitis Ulcer	50 (19.5%)	15 (23.8%)	38 (15.0%)
Hirsutism	6 (2.3%)	7 (11.1%)	36 (14.2%) **
Fever	39 (15.2%)	9 (14.3%)	36 (14.2%)
Depression	33 (12.9%)	5 (7.9%)	35 (13.8%)
Alopecia	48 (18.8%)	7 (11.1%)	35 (13.8%)
Infection	37 (14.5%)	18 (28.6%)	26 (10.3%)
Sinusitis	33 (12.9%)	4 (6.3%)	22 (8.7%)
Pain Chest	27 (10.5%)	5 (7.9%)	22 (8.7%)

*Frequency > 10% in either GL701 200 mg or placebo patients.
** P< 0.05, Placebo vs. GL701 200 mg

For adverse events occurring in < 10% of patients, the following showed an absolute difference of at least 3% between placebo or GL701 200 mg, or, if less than 3% difference, the difference was significant ($p < 0.05$).

Table 7-4: Adverse events with frequency <10% and at least a 3% or a significant difference (GL94-01 and GL95-02)

COSTART TERM	Placebo N=256	GL701 200 mg N=253
Back Pain	16 (6.3%)	24 (9.5%)
Hypertension	7 (2.7%)	20 (7.9%) **
Lymphadenopathy	21 (8.2%)	12 (4.7%)
Dyspnea	22 (8.6%)	11 (4.3%)
Hematuria	1 (0.4%)	9 (3.6%) **
Pharyngitis	14 (5.5%)	6 (2.4%)
Creatinine Increase	0 (0.0%)	6 (2.4%)**
Nasal Septum Disorder (nasal ulcers)	14 (5.5%)	5 (2.0%) **
Joint Disorder	14 (5.5%)	4 (1.6%) **
Rash Lupus Erythematosus	13 (5.1%)	4 (1.6%) **
Anorexia	10 (3.9%)	2 (0.8%) **

** P< 0.05, Placebo vs. GL701 200 mg

Adverse events that were significantly more common in GL701 200 mg-treated patients were acne, hirsutism, hypertension, hematuria, and increased creatinine. Acne and hirsutism were expected androgenic events; and the difference between placebo and GL701 was clinically meaningful as well as statistically significant. Hematuria, hypertension, and creatinine increase were statistically significantly more frequent in the GL701 group, but due to the relatively small numbers of patients in whom these were reported, their clinical significance, if any, is less clear. These adverse events, along with acne and hirsutism, are analyzed and discussed in more detail in **Section 7.4**.

Patients treated with placebo had statistically significantly higher incidences of myalgia, joint disorder, anorexia, nasal ulcers and LE skin rash. Some of these differences are possibly explainable by decreases in SLE manifestations reported as adverse events in the GL701 group.

The pattern of adverse events in the Taiwan study showed a similar, but not identical pattern. Adverse events reported by at least 10% of the patients in either treatment group from the Taiwan study are summarized in **Table 7-5**. Acne was the most common adverse event in the Taiwan study, and, in fact, was more prevalent in both the placebo and GL701 groups than in the US studies. This may reflect the fact that almost all patients in the Taiwan study were also receiving co-treatment with corticosteroids. Additionally, this may reflect racial differences in sensitivity to an androgenic drug. By contrast, hirsutism which had been reported in approximately 15% of GL701 patients in the double-blind trials in the United States was not reported at all in either placebo or GL701 patients in the Taiwan study.

Table 7-5: Adverse Events Reported by at Least 10% in Either Treatment Group (GBL96-01)

	Placebo N= 59	**GL701 N= 61**
Arthralgia	37 (62.7%)	39 (63.9%)
Acne *	17 (28.8%)	36 (59.0%)*
Pharyngitis	32 (54.2%)	34 (55.7%)
Myalgia	24 (40.7%)	28 (45.9%)
Headache *	37 (62.7%)	26 (42.6%)*
Pain Abdomen	25 (42.4%)	23 (37.7%)
Asthenia	19 (32.2%)	18 (29.5%)
Cough Increase	18 (30.5%)	18 (29.5%)
Dizziness	19 (32.2%)	15 (24.6%)
Pain Chest	11 (18.6%)	14 (23.0%)
Dyspnea	8 (13.6%)	14 (23.0%)
Rash	16 (27.1%)	14 (23.0%)
Fever	17 (28.8%)	13 (21.3%)
Alopecia	8 (13.6%)	13 (21.3%)
Pain	8 (13.6%)	11 (18.0%)
Diarrhea	11 (18.6%)	11 (18.0%)
Rhinitis	13 (22.0%)	11 (18.0%)
Stomatitis Ulcer	17 (28.8%)	10 (16.4%)
Pain Back	10 (16.9%)	9 (14.8%)
Edema	6 (10.2%)	9 (14.8%)
Injury Accident	6 (10.2%)	8 (13.1%)
Insomnia	7 (11.9%)	8 (13.1%)
Pruritus	7 (11.9%)	8 (13.1%)
Infection*	15 (25.4%)	6 (9.8%)*
Dry Eye	10 (16.9%)	6 (9.8%)
Vomit	8 (13.6%)	5 (8.2%)
Peripheral Edema	8 (13.6%)	5 (8.2%)
Rash Lupus Erythematosus	7 (11.9%)	5 (8.2%)
Conjunctivitis	7 (11.9%)	5 (8.2%)
Nausea	9 (15.3%)	4 (6.6%)

*P-value<0.05, GL701 vs. Placebo, chi-square test

Of the adverse events reported by at least 10% of the patients, acne was the only event statistically significantly more frequent in the GL701 group as compared to the placebo group. Headache and infection were statistically significantly more frequent in the placebo group compared with the GL701 group. Of the adverse events reported with an incidence of less than 10%, the only statistically significant difference was for seborrhea (0 placebo vs. 5 GL701 patients).

7.2.2 Severe Adverse Events

Adverse events that were assessed as "severe" occurred in similar frequencies in both treatment and placebo groups, with asthenia being the most common adverse event reported as severe in both placebo and GL701 treated patients. Although the patient numbers are small, abdominal pain reported as a severe adverse event occurred in 6 GL701 200 mg patients, 2 GL701 100mg patients, and no placebo patients. Severe adverse events reported as abdominal pain are analyzed and discussed in more detail in **Section 7.4**. There appeared to be no meaningful differences between treatment groups for other severe adverse events. In the Taiwan study, only four severe events (fever, headache, abdominal pain, and vomiting) occurred in at least 5% of either treatment group. These occurrences were only found in the placebo group.

Table 7-6: Severe adverse events occurring in at least 2 patients* (GL94-01 and GL95-02)

COSTART TERM	Placebo N=256	GL701 100 mg N=63	GL701 200 mg N=253
Asthenia	22 (8.6%)	4 (6.3%)	22 (8.7%)
Headache	11 (4.3%)	1 (1.6%)	8(3.2%)
Arthralgia	6 (2.3%)	3 (4.8%)	6 (2.4%)
Pain Abdomen	0 (0%)	2 (3.2%)	6 (2.4%)
Rash	5 (2.0%)	1 (1.6%)	6 (2.4%)
Arthritis	2 (0.8%)	3 (4.8%)	5 (2.0%)
Dyspnea	1 (0.4%)	0 (0%)	4 (1.6%)
Depression	4 (1.6%)	1 (1.6%)	2 (0.8%)
Diabetes Mellitus	0 (0%)	0 (0%)	2 (0.8%)
Emotional Lability	0 (0%)	0 (0%)	2 (0.8%)
Infection	0 (0%)	4 (6.3%)	2 (0.8%)
Myalgia	5 (2.0%)	1 (1.6%)	2 (0.8%)
Pain	1 (0.4%)	0 (0%)	2 (0.8%)
Pain Chest	4 (1.6%)	1 (1.6%)	2 (0.8%)
Paresthesia	1 (0.4%)	0 (0%)	2 (0.8%)
Pleural Disorder	1 (0.4%)	0 (0%)	2 (0.8%)
Vasculitis	0 (0%)	1 (1.6%)	2 (0.8%)
Joint Disorder	2 (0.8%)	0 (0%)	1 (0.4%)
Peripheral Edema	2 (0.8%)	2 (3.2%)	0 (0%)
Sepsis	2 (0.8%)	0 (0%)	0 (0%)
Cyst	2 (0.8%)	0 (0%)	0 (0%)
Thinking Abnormal	2 (0.8%)	0 (0%)	0 (0%)

*Frequency at least 2 patients in either GL701 200 mg or placebo

7.2.3 Relationship of Adverse Events and Duration of Exposure to GL701

In order to determine whether there were any adverse events which increased in frequency with longer duration on study drug, or appeared late in the course of therapy, adverse event rates were pooled longitudinally for the double-blind placebo-controlled studies (GL94-01 and GL95-02) and the open-label extension study (GL95-01). Because of possible selection bias for patients entering the open-label study from the prior double-blind studies, a longitudinal analysis of time to first occurrence of adverse event using the life-table method is presented in **Table 7-7** for selected events. This analysis provides incidence rates by exposure to GL701 and shows that there are no adverse events whose incidence rates appeared to increase meaningfully with increased duration of exposure to GL701. The denominator is the number of patients at risk during the defined time period. For example, in the interval from 183-365 days the number of patients at risk for acne equals the number of patients treated in that interval minus those who previously experienced acne. For hirsutism, there are more patients at risk in the interval from 183-365 days as compared to the number of patients at risk in the same interval for acne (353 patients for hirsutism vs. 269 patients for acne). This is due to a fewer number of patients experiencing their first occurrence of hirsutism in the first time interval (1-182 days) as compared to acne (40 patients with hirsutism vs. 152 patients with acne).

Table 7-7: Time to First AE (Life Table Method*) in GL701-treated Patients (GL94-01, GL95-02 and GL95-01)

	1-182 days			183-365 days			366-547 days			> 547 days		
COSTART	**N**	**N**	**%**	**N**	**N**	**%**	**N**	**N**	**%**	**N**	**N**	**%**
Acne	152	493	(30.8)	38	269	(6.7)	10	156	(6.4)	2	76	(2.6)
Hirsutism	40	493	(8.1)	12	353	(3.4)	6	213	(2.8)	1	112	(0.9)
Menorrhagia	11	493	(2.2)	2	379	(0.5)	2	234	(0.9)	1	130	(0.8)
Metrorrhagia	25	493	(5.1)	4	364	(1.1)	6	223	(2.7)	1	123	(0.8)
Hypertension	17	493	(3.4)	5	373	(1.3)	1	225	(0.9)	0	130	(0.0)
Hematuria	12	493	(2.4)	3	378	(0.8)	1	236	(0.4)	3	134	(2.2)
Alopecia	46	493	(9.3)	18	351	(5.1)	6	208	(2.9)	2	114	(1.8)
Dyspnea	13	493	(2.6)	7	378	(1.9)	3	228	(1.3)	0	130	(0.0)
Lymphadenopathy	14	493	(2.8)	4	374	(1.1)	2	229	(0.9)	1	129	(0.8)
Myalgia	63	493	(12.8)	26	338	(7.7)	4	192	(2.1)	5	106	(4.7)

*This table used the life table method: **N**=number of patients experiencing first AE in the time category, **N**=number of patients at risk in the time category, %=(N/N)*100.

Acne and hirsutism were the most frequently reported adverse event with GL701 and were more likely to be reported early in treatment. Patients who had not developed these adverse events in the first 6 months of exposure, appeared less likely to develop them later. There were no adverse events that increased in frequency with longer duration of treatment with GL701.

7.2.4 Early Termination from Study Drug

In GL94-01 and GL95-02, approximately 25% of the placebo group, 27% of the GL701 100 mg group, and 32% of the GL701 200 mg group terminated early. Early terminations, assessed by the investigator as being for safety, accounted for the difference in early terminations between the GL701 200 mg and placebo groups.

Table 7-8: Premature terminations of study drug (GL94-01 and GL95-02)

Reason For Early Termination*	Placebo	GL701 100 mg	GL701 200 mg
Total evaluated	256	63	253
Total discontinuing prematurely	65 (25.4%)	17 (27.0%)	82 (32.4%)
Lack of efficacy	16 (6.3%)	6 (9.5%)	16 (6.3%)
Possibly related to safety**	21 (8.2%)	4 (6.3%)	37 (14.6%)
Other	28 (10.9%)	7 (11.1%)	29 (11.5%)

*Classification according to investigator assessment of principal termination reason.
**Includes patients with adverse events leading to termination, but not attributed to study treatment by investigator.

Provided in **Appendix 7** is a listing of the individual reasons for early termination for patients terminating due to adverse events or otherwise assessed by the investigator as terminating for safety concerns. A number of patients had more than one reason or adverse event listed as a reason for termination. Acne and/or hirsutism were the most common reasons for discontinuation for reasons possibly related to safety, and accounted for approximately half of the difference in safety related terminations in the GL701 group. Twelve women dropped out due to acne or hirsutism while on GL701 compared with only one in the placebo group. However, none of these events was assessed as severe.

There appeared to be no other clear-cut pattern in the other reasons for premature terminations in either placebo or GL701 treatment groups. In both the GL701 200 mg and placebo groups, a number of events that probably reflect their underlying SLE, such as increased fatigue, disorders of affect, especially depression, SLE rashes or myalgia, led to discontinuation. In both groups, weight gain or fluid retention and menstrual abnormalities or hot flashes also led to premature termination.

A few of the events leading to termination may be considered to have been medically serious. In the GL701 group, single instances of hepatitis C, GI bleed, psychosis, pulmonary edema and renal deterioration led to discontinuation. In the placebo group, two instances of septicemia and single instances of hepatitis, suicidal depression, pneumonia, coronary artery spasm, carcinoma of the lung and pseudotumor cerebri led to discontinuation. Additionally, four deaths, all in the placebo group, were the

reason for termination from study drug. These were suicide in two patients, pulmonary hypertension and sudden death.

7.2.5 Deaths

There were no deaths during the treatment phase of Study GL94-01, but three deaths occurred in the follow-up period; none appeared to be related to previous treatment with study drug (**Table 7-9**). There were no deaths in patients who received GL701 in study GL95-02, but 5 patients in the placebo group died, 4 while on treatment. These 4 deaths on study were suicide in two, sudden death, and pulmonary fibrosis. Three patients died while on study in the open-label extension study, GL95-01; one each from metastatic carcinoma, cerebrovascular acccident and fibrinous endocarditis. Two additional patients died in the follow-up period of that study.

Table 7-9: Deaths during or following termination of study drug treatment (GL94-01, GL95-02 and GL95-01)

Study	Patient ID #	Cause Of Death	Drug	Duration Of Exposure To Study Drug (days)	Interval Between Discontinuation Of Study Drug And Death
GL94-01	27206	Respiratory failure and massive bleeding.	Placebo	125	2 months post study
GL94-01	12113	Respiratory failure and thrombotic microangiopathy	GL701 100 mg	95	14 weeks post study
GL94-01	13103	Pancreatitis	GL701 200 mg	160	9 months post study
GL95-02	20511	Pulmonary hypertension/restrictive lung disease	Placebo	206	on study
GL95-02	48817	Sudden Death	Placebo	80	on study
GL95-02	35712	Suicide	Placebo	5	on study
GL95-02	37495	Suicide	Placebo	177	on study
GL95-02	36571	Non-Hodgkin's lymphoma	Placebo	348	6 weeks post study
GL95-01	18029	Metastatic carcinoid tumor	GL701	322	1 day post-study
GL95-01	18035	Carcinoma of the breast	GL701	362	15 months post study
GL95-01	12005	Cardiac arrest – sudden death	GL701	372	35 days post study
GL95-01	25003	Fibrinous endocarditis and lupus nephritis	GL701	359	1 day post study
GL95-01	25005	Cereberovascular accident	GL701	539	On study
GL95-01	27001	Exacerbation of COPD – pulmonary insufficiency	GL701	463	24 days post study

There were no deaths in the Taiwan study.

7.2.6 Other Serious Adverse Events

Serious adverse events occurred in 39 GL701 200 mg, 7 GL701 100 mg, and 47 placebo patients participating in GL94-01 and GL95-02. However, only 3 serious adverse events were considered possibly related, 2 in the placebo group (one suicide and one patient with menomettrorhagia) and one in GL701 200 mg (a patient with an acute psychosis).

In the Taiwan study, serious adverse events were reported in a significantly higher proportion of patients in the placebo group than in the GL701 group. One or more serious adverse events were reported in 7 of 61 patients (11.5%) and 18 of 59 patients (30.5%) in the GL701 and placebo groups, respectively; the difference was statistically significant (P = 0.010, chi-square test). In most cases, the types of serious adverse events reported were consistent with SLE flares or hospitalization for manifestations of SLE rather than adverse effects of the study drug.

7.3 CLINICAL LABORATORY EVALUATION

7.3.1 Hematology

There were no clinically meaningful differences in mean changes from baseline between treatment groups for any of the hematology parameters in either the pooled GL94-01 and GL95-02 studies or the Taiwan study.

7.3.2 Liver Function Tests

There were no changes of potential significance in liver function tests (ALT, AST, alkaline phosphatase, or total bilirubin) within and between the treatment groups (**Table 7-10**). Equally, serum calcium, phosphorus, uric acid, total protein and albumin showed no clinically relevant differences between treatment groups, or changes from baseline.

Table 7-10: Mean (Median) change in liver function tests (GL94-01 and GL95-02)

	Placebo N = 240	**GL701 100 mg N = 63**	**GL701 200 mg N = 232**
Total Bilirubin (mg/dl)			
Baseline	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Change	-0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Alkaline Phosphatase (IU/L)			
Baseline	61.9 (57.0)	61.3 (57.0)	63.3 (62.0)
Change	1.4 (2.0)	1.2 (2.0)	2.3 (1.0)
ALT (SGPT) (IU/L)			

Baseline	21.8 (18.0)	20.9 (19.0)	21.2 (18.0)
Change	-0.0 (1.0)	2.6 (0.0)	-0.8 (-1.0)
AST (SGOT) (IU/L)			
Baseline	22.6 (20.0)	20.9 (19.0)	22.9 (21.0)
Change	0.8 (1.0)	1.7 (1.0)	0.0 (-1.0)

In the Taiwan study, there were no clinically significant differences in liver function tests though the placebo group demonstrated increases in SGOT and SGPT.

7.3.3 Renal Function Tests

BUN and creatinine levels did not change during study and were similar within or between treatment groups (**Table 7-11**). Mean changes in 24-hour urine protein excretion increased in all treatment groups, but to a greater extent in GL701 patients. However, a few patients with very high values impacted 24-hour urine protein; and median changes were only slightly higher in the GL701 groups.

Table 7-11: Mean (Median) Change in Renal Function (GL94-01 and GL95-02)

	Placebo N = 240	**GL701 100 mg N = 63**	**GL701 200 mg N = 233**
BUN (mg/dl)			
Baseline	13.8 (13.0)	18.2 (15.0)	14.6 (13.0)
Last Visit	13.7 (13.0)	18.9 (13.0)	14.6 (13.0)
Change	-0.1 (0.0)	0.7 (-1.0)	0.0 (0.0)
Creatinine (mg/dl)			
Baseline	1.0 (1.0)	1.2 (1.0)	1.1 (1.0)
Last Visit	1.0 (1.0)	1.3 (1.1)	1.1 (1.0)
Change	0.0 (0.0)	0.1 (0.0)	0.0 (0.0)
24-hour urine Protein (mg/24hr)			
N	N = 229	N = 52	N = 214
Baseline	322.7 (158.0)	715.3 (257.0)	396.1 (166.0)
Last Visit	367.6 (163.0)	1040 (269.5)	725.5 (198.5)
Change	44.9 (4.0)	324.9 (69.0)	329.4 (23.0)

A shift table for 24-hour urine protein shows that approximately 21% of placebo patients went from normal to high (> 150 mg/24hr), compared to 22% of GL701 200 mg patients (**Table 7-12**). Proteinuria is analyzed and discussed in more detail in **Section 7.4**.

Table 7-12: Changes in 24-hour urine protein (GL94-01 and GL95-02)

	LAST VISIT			
	Normal		High	
BASELINE VISIT	Placebo	GL701	Placebo	GL701
Normal	64 (27.9%)	44 (20.6%)	47 (20.5%)	48 (22.4%)
High	37 (16.2%)	26 (12.1%)	81 (35.4%)	96 (44.9%)

Likewise, in the Taiwan study, there were no differences between treatment groups (**Table 7-13**). Twenty-four hour urine protein was not collected.

Table 7-13: Mean (Median) Change in Renal Function (GBL96-01)

	Placebo	**GL701 200 mg**
BUN (mg/dl)		
Baseline	14.4 (12.8)	17.3 (13.8)
Change from Baseline at Last Visit	2.5 (0.5)	1.7 (0.1)
Creatinine (mg/dl)		
Baseline	0.8 (0.8)	1.0 (0.7)
Change from Baseline at Last Visit	0.0 (0.0)	0.2 (0.0)

Creatinine showed a mean increase from baseline of 0.2 mg/dl (an increase of 2.8%) in the GL701 treatment group. However, the mean was influenced by one patient with an increase of 6.1 mg/dl and the group median change was 0.0 mg/dl. No patient in the GL701 treatment group had a shift from a normal baseline value to a high value at final visit.

7.3.4 Serum Glucose

Minor changes were noted in glucose levels during study GL94-01. In that study, glucose levels tended to increase in the placebo group, compared to the GL701 group. This finding was not confirmed in study GL95-02, and probably reflects changes in serum glucose levels due to fluctuations in prednisone dose. Additionally, glycosylated hemoglobin (HbA1c) was measured only in Study GL95-02, but there was no difference between placebo and GL701 noted in that study.

7.3.5 Urinalysis

With respect to urinalysis, there was no meaningful mean or median change in the WBCs or RBCs from baseline. A shift table shows slightly more patients with a change from normal to high (> 5 RBC/hpf) in RBCs in patients treated with GL701 (**Table 7-14**). The significance of this is unclear, especially since urine collections were not necessarily delayed because of menses and were collected even if a urinary

tract infection was present at a study visit. Hematuria, as a finding in urinalyses and as an adverse event, is analyzed and discussed in more detail in **Section 7.4**.

Table 7-14: Changes in Urine RBC
(GL94-01 and GL95-02)

	LAST VISIT			
	Normal		**High**	
Baseline Visit	Placebo	GL701	Placebo	GL701
Normal	193 (83.9%)	173 (77.9%)	15 (6.5%)	28 (12.6%)
High	18 (7.8%)	10 (4.5%)	4 (1.7%)	11 (5.0%)

7.3.6 Serum Complement, Anti DS DNA

As shown in the **Figure 7-1** below, C3 serum complement declined in both treatment arms in the double-blind studies, but the reduction from baseline was greater in the GL701 group compared with placebo. The follow-up data during the open-label extension (study GL95-01) for change in serum C3 complement is consistent with the independent findings from the two double-blind studies. The figure also demonstrates that most of the reduction occurred by month 3 of treatment, or earlier, with relatively little further progressive decrease in the subsequent 9 months. Similarly, there was a similar early decrease in C3 for patients previously treated with placebo in the double-blind studies who received GL701 for the first time in the open-label study. This was evident at Months 6 and 12 (the protocol did not specify measurement of complement at Months 3 and 9). For patients who had received GL701 in the double-blind studies, there was an additional small decline in C3, which continued into the open-label study.

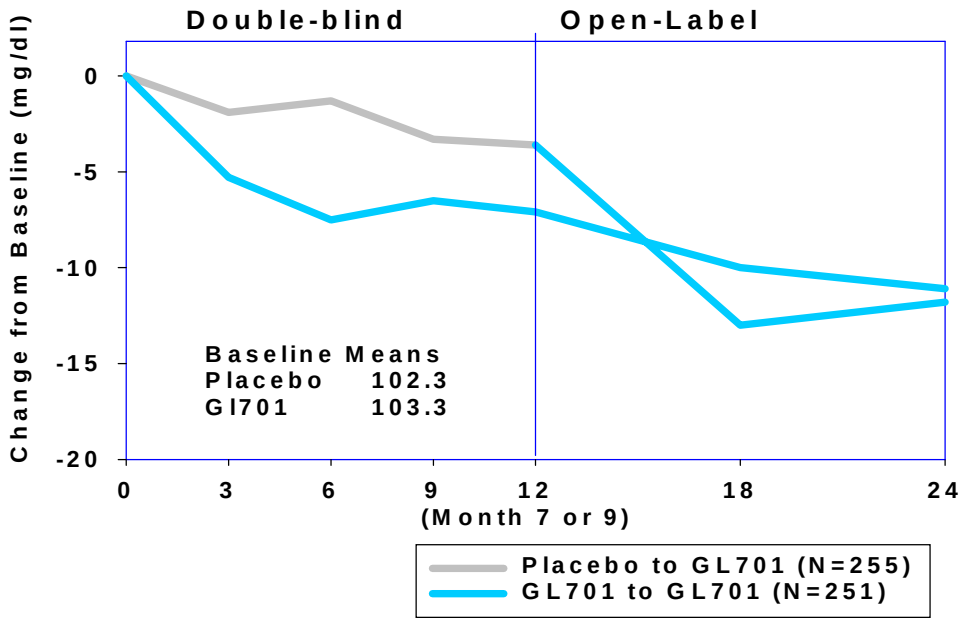


Figure 7-1: Mean Change from Baseline in C3 Complement

There were no meaningful differences between groups for C4 or anti-double stranded DNA antibody, but C4 decreased slightly and ds-DNA increased slightly in all treatment groups.

Table 7-15: Mean (Median) change in serum complement and anti-ds DNA (GL94-01 and GL95-02)

	Placebo N = 240	**GL701 100 mg N = 63**	**GL701 200 mg N = 233**
C4 (mg/dl)			
Baseline	18.1 (16.0)	17.6 (15.0)	18.3 (17.0)
Last Visit	17.3 (16.0)	16.1 (13.0)	17.0 (16.0)
Change	-0.7 (0.0)	-1.5 (-1.0)	-1.3 (-1.0)
Anti ds-DNA (IU/ml)			
Baseline	25.6 (2.4)	87.9 (5.9)	42.4 (3.1)
Last Visit	38.7 (2.4)	118.2 (5.8)	52.3 (3.0)
Change	13.1 (0.0)	30.3 (0.0)	9.9 (0.0)

Approximately 30% of the GL701 group, and 32% of the placebo group had low C3 values at baseline. **Table 7-16** below shows that at the last scheduled visit, 16% of patients on GL701 200 mg had gone from normal to low C3 (< 85 mg/dl), compared to 6% of placebo patients.

Table 7-16: Changes in C3
(GL94-01 and GL95-02)

	Low	Low	Normal	Normal	Normal	High
	Low	**Normal**	**Low**	**Normal**	**High**	**Normal**
Placebo	60 (25.0%)	16 (6.7%)	14 (5.8%)	149 (62.1%)	1 (<1%)	0 (0.0%)
GL701 200 mg	61 (26.2%)	8 (3.4%)	36 (15.5%)	125 (53.6%)	1 (<1%)	2 (<1%)

There were no clinically meaningful changes in either mean/median or shift changes for C4 complement.

Similar changes in C3, C4, DS-DNA were also noted in the Taiwan study (**Table 7-17**).

Table 7-17: Mean (Median) Change in Serum Complement and Anti-ds DNA
(GBL96-01)

	Placebo	GL701 200 mg
C3 (mg/dl)	**N=59**	**N=59**
Baseline	72.4 (65.9)	76.7 (70.0)
Change from Baseline at Last Visit	0.5 (2.2)	-10.3 (-7.0)
C4 (mg/dl)	**N=59**	**N=61**
Baseline	13.3 (11.6)	16.6 (13.0)
Change from Baseline at Last Visit	0.7 (-0.1)	-1.8 (-1.0)
Anti ds DNA (IU/ml)	**N=59**	**N=60**
Baseline	180.2 (79.0)	150.9 (59.9)
Change from Baseline at Last Visit	-80.1 (-6.5)	-1.8 (-1.7)

7.3.7 Serum Lipids

As shown in **Figure 7-2** below, total cholesterol, HDL-C and LDL-C decreased in all treatment groups, but the decrease in LDL-C was relatively small. The decreases in total cholesterol and HDL-C were greater in the GL701 groups than in the placebo group. The ratio of total cholesterol to HDL-C increased slightly in the placebo group, and increased approximately 10% in the GL701 groups. Serum triglycerides were substantially decreased in the GL701 groups, but increased in the placebo group; the difference between GL701 groups and placebo was significant. There was no apparent dose response relationship between GL701 100 mg or GL701 200 mg for any of these lipid measurements.

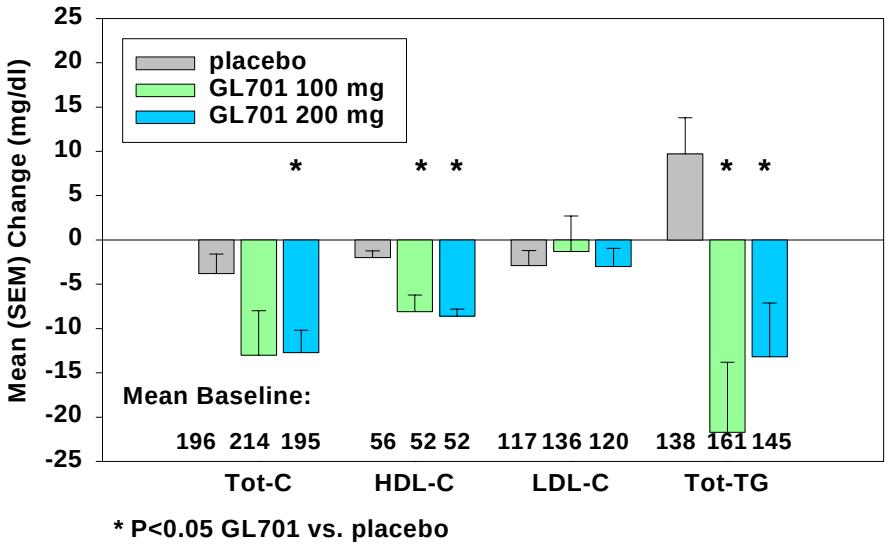


Figure 7-2: Mean Changes in Serum Lipids (GL94-01 and GL95-02)

As shown in **Figure 7-3** below, the pooled data and follow-up data during the open-label extension (study GL95-01) for change in HDL-C demonstrate that most of the reduction in serum HDL-C occurred by month 3 of treatment, or earlier, with relatively little further progressive decrease in the subsequent 9 months. A similar pattern is seen with triglycerides, and total cholesterol.

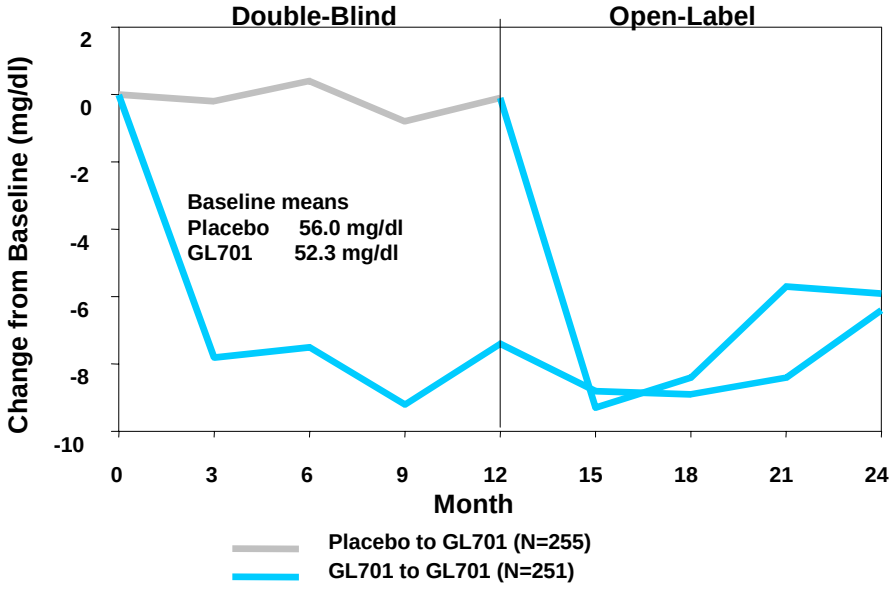


Figure 7-3: Mean Changes in HDL-C

Although only total cholesterol and triglycerides were measured in the Taiwan study, the findings were similar. Total cholesterol and triglycerides decreased in the GL701 treatment group in comparison to placebo.

Table 7-18: Summary of Total Cholesterol and Triglycerides (GBL96-01)

	Total Cholesterol (mg/dl)		Triglycerides (mg/dl)	
Treatment Group	**Baseline**	**Last Visit Change**	**Baseline**	**Last Visit Change**
Placebo				
Mean	179.7	12.5	111.0	-1.4
Median	174.0	8.0	101.0	-5.0
GL701 200 mg				
Mean	183.7	-10.2	122.2	-28.4
Median	167.0	-9.3	97.0	-31.7

Current guidelines (NCEP: NIH, 1994) call for HDL-C to be maintained $\geq$ 35 mg/dl. The following analysis (**Table 7-19**) presents percent of patients in the pooled double-blind studies in whom HDL-C went from normal to low (< 35 mg/dl). Approximately 17% of patients in the GL701 200 mg went from normal to low, compared to 7% in the placebo group.

Table 7-19: Changes in HDL-C (GL94-01 and GL95-02)

	N	Low-Low	Low-Normal	Normal-Low	Normal-Normal	Normal-High	High-Normal	High-High
Placebo	237	9 (3.8%)	6 (2.5%)	16 (6.8%)	186 (78.5%)	5 (2.1%)	9 (3.8%)	6 (2.5%)
GL701 200mg	226	20 (8.8%)	5 (2.2%)	39 (17.3%)	157 (69.5%)	0 (0.0%)	4 (1.8%)	1 (0.4%)

7.3.8 Serum Hormone Levels

7.3.8.1 Serum Hormone Levels in Normal Volunteers

The most reliable data for evaluating the effects of GL701 on sex hormones comes from the pharmacokinetic studies in healthy subjects, where hormone levels were obtained under controlled conditions, without the complicating factors of concomitant medications such as birth control pills or hormone replacement therapy. In addition, in pre-menopausal women, samples were obtained with specific timing in relation to the menstrual cycle.

7.3.8.2 Pre-Menopausal Healthy Women

In Study GL96-02, a pharmacokinetic and prednisone interaction study, normal pre-menopausal healthy volunteers received GL701 for 28 days. Sampling was timed in the menstrual cycle to coincide with nadir

levels of estrogens and blood levels were obtained at baseline and after 28 days of dosing. The 28 day sample was a trough sample, 24 hours post-last dose. In these pre-menopausal women, mean testosterone levels increased significantly, approximately 27% and mean serum hormone binding globulin (SHBG) decreased significantly, approximately 40%. There was an approximately 20% increase in both estradiol and estrone, but these changes were not statistically significant (**Table 7-20**).

Table 7-20
Changes in Serum Hormone Levels
Study GL96-01- Healthy Pre-Menopausal Volunteers

Hormones	**Baseline N = 14**	**Post 28 days GL701 N = 14**	
	Mean (SD)*	**Mean (SD)**	**P-value**
Estradiol (ng/dl)	3.5 (1.8)	4.2 (3.1)	N.s.
Estrone (ng/dl)	3.7 (1.0)	4.5 (1.7)	N.s.
Androstenedione (ng/dl)	149 (52)	195 (43)	0.009
Testosterone (ng/dl)	33.0 (9.9)	41.9 (10.8)	0.021
SHBG (μg/dl)	1.7 (0.7)	1.0 (0.5)	0.001
Progesterone (ng/dl)	46.4 (15.0)	46.0 (15.0)	N.s.

7.3.8.3 Post-Menopausal Healthy Women

In Study GL99-01, a pharmacokinetic and bioequivalence study, normal post-menopausal volunteers received GL701 for 7 days. Blood levels were obtained at baseline and after 7 days of dosing. The 7-day sample was a trough sample, 24 hours post-last dose. There was an approximately 100% increase in mean testosterone levels, while estradiol levels increased about 20%.

Table 7-21
Changes in Serum Hormone Levels
Study GL99-01- Healthy Post-Menopausal Volunteers

Hormones	**Baseline**	**Post 7 days GL701**	
	Mean (SD)	**Mean (SD)**	**P-value**
Estradiol (pg/ml)	8.50 (5.17)	11.5 (6.66)	0.001
Testosterone (ng/dl)	24.5 (12.9)	48.7 (20.2)	0.001

7.3.8.4 Serum Hormone Levels in Patients with SLE

Serum hormone levels were collected at baseline and at the end of dosing in Studies GL94-01 and GL95-02. Thus, the data reflect up to 9 months of study drug in GL94-01 and up to one year in GL95-02. The data regarding hormone levels obtained from these placebo-controlled studies in patients with SLE may be less reliable than data from healthy volunteers, because confounding factors, such as timing with

respect to menses and concomitant hormonal therapy, could not be controlled. Also, the timing from last dose of study drug to collection of blood sample was not well controlled. Nevertheless, the findings with respect to sex hormone levels are generally consistent with the volunteer studies. In GL701 patients, there were predictable increases in testosterone levels and decreases in SHBG, while there were small increases in mean estradiol levels, but there was also a great deal of variability.

A. Sex Hormone Binding Globulin (SHBG)

SHBG was measured only in Study GL95-02. In Study GL95-02, mean SHBG decreased approximately 42% in the GL701 group, while remaining unchanged in the placebo group.

B. Testosterone

In patients with SLE, serum testosterone increased in an apparently dose-related fashion in the GL701 groups, and remained unchanged in the placebo group. These results appeared similar in both pre- and post-menopausal women. There was more than a 200% increase in testosterone in pre-menopausal patients receiving GL701 200 mg, and more than 300% in post-menopausal patients. Nevertheless, mean levels remained within the upper limits of normal, but some patients exceeded the upper limits of normal. Thirty-three patients in the GL701 groups compared to none in the placebo group went from "low to high" or "normal to high" (> 110 ng/dl) at baseline to last visit

Table 7-22: Change in testosterone levels (ng/dl) by menopausal status (GL94-01 and GL95-02)

	Baseline	Last Visit	Change
	Mean (Median)	**Mean (Median)**	**Mean (Median)**
Pre-Menopausal			
Placebo (N=101)	20.2 (16.0)	18.9 (15.0)	-1.4 (-1.0)
GL701 100 mg (N=41)	19.3 (16.0)	32.6 (33.0)	13.3 (16.0)
GL701 200 mg (N=115)	21.6 (17.0)	65.1 (61.0)	43.5 (38.0)
Post-Menopausal			
Placebo (N=87)	18.4 (11.0)	17.8 (11.0)	-0.6 (0.0)
GL701 100 mg (N=19)	11.2 (6.0)	52.6 (48.0)	41.4 (35.0)
GL701 200 mg (N=63)	16.7 (11.0)	75.6 (54.0)	58.9 (42.0)

The increases in serum testosterone noted at last visit in SLE patients receiving GL701 were greater than the increases noted in healthy pre- or post-menopausal volunteers. The SLE patients received GL701 usually for 7 to 12 months, while the volunteers received GL701 for only 7 or 28 days. These data suggest either that SLE patients metabolize GL701 differently than healthy subjects, or that it may take

longer than one month for testosterone levels following GL701 administration to reach "steady state" levels.

7.3.8.5 Estradiol

A. Pre-menopausal Patients

In the GL701 200 mg group, mean serum levels of estradiol increased slightly, less than 10% or 7.0 pg/ml, compared to a small decrease, -3.1 pg/ml, in the GL701 100 mg and placebo groups. However, interpretation of serum estradiol levels is difficult in these pre-menopausal women because serum sampling was not timed to coincide with menstrual cycles. Nevertheless, changes in estradiol concentrations were within the expected ranges of cyclical circulating estradiol levels, and are consistent with the small increases noted in pre-menopausal volunteers.

B. Post-menopausal Patients

In post-menopausal women estradiol levels increased in the GL701 groups and the increase was greater in the GL701 200 mg group, though the interpretation of these results is confounded by the use of hormone replacement therapy in some patients and by the different baseline values in the two groups. The high baseline estradiol levels in both groups suggest that many of these patients, although designated as post-menopausal by the investigator, were either peri-menopausal (which is known to have high estradiol levels) or were taking hormone replacement therapy.

Changes in estradiol levels in post-menopausal women receiving HRT are displayed in **Figure 7-4** below; note median values are represented by the solid horizontal bars. Although there was an increase in estradiol levels in the GL701 patients compared to placebo patients, these women had had high baseline levels, in the range expected for HRT, and the small increment over baseline noted in the GL701 patients would not be expected to have a clinically significant impact.

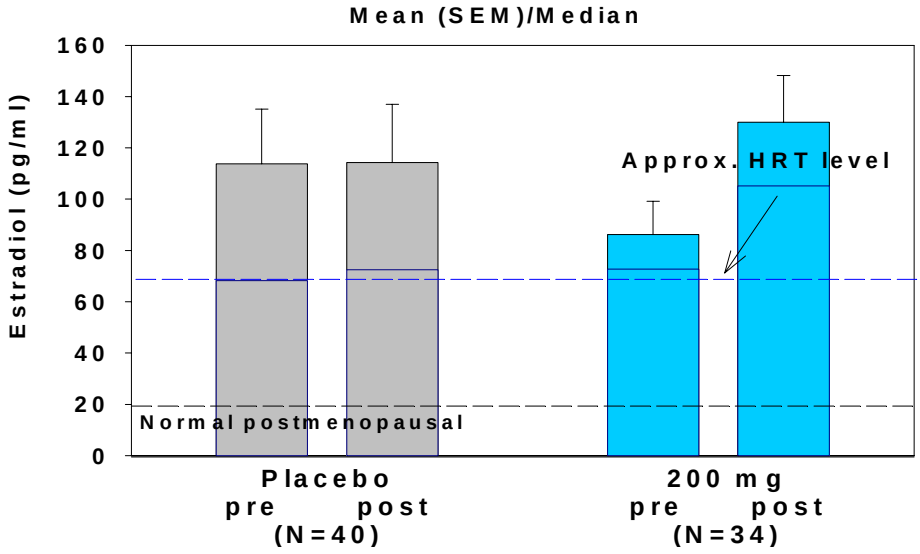


Figure 7-4: Estradiol Levels in Women on HRT Pre and Post Treatment with GL701 (GL94-01 and GL95-02)

Changes in estradiol levels in post-menopausal women not receiving HRT and whose baseline estradiol was < 25 pg/ml are shown in **Figure 7-5**, note median values are represented by solid horizontal bars. Increases in estradiol in the GL701 patients led to mean levels in the range of approximately 50 pg/ml, or median levels of approximately 30 pg/ml. These levels are substantially lower than the baseline values for the patients receiving HRT shown in **Figure 7-4** above, and lower than or similar to HRT. Only 3 patients in this group, 2 GL701 100 mg and 1 GL701 200 mg patients, had estradiol levels > 70 pg/ml at last visit, ranging from 179 to 376 pg/ml. These 3 patients had a large impact on the means. No adverse events or other findings related to increased estradiol levels were noted.

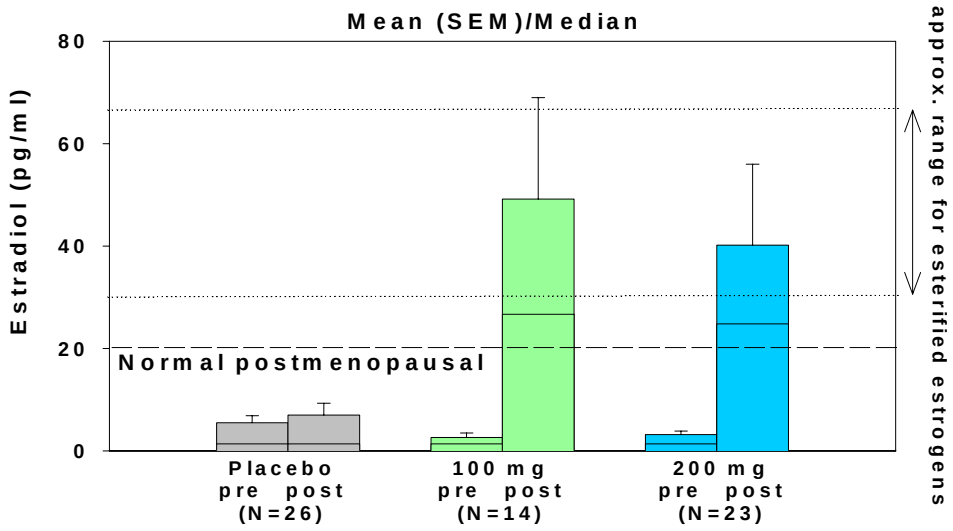


Figure 7-5: Estradiol Levels Pre and Post Treatment for Post-menopausal Women with Baseline Estradiol < 25 pg/ml

7.4 SAFETY ISSUES OF POTENTIAL CONCERN

7.4.1 Acne and Hirsutism

The most common adverse events associated with GL701 were acne and hirsutism, both apparently secondary to androgenic activity of DHEA or its metabolites. In the placebo-controlled trials with GL701, these two adverse events were consistently more frequent in the GL701 group. In the pooled placebo-controlled data, acne was reported in greater than 35% of patients in the GL701 groups, compared to approximately 15% of placebo patients. However, although it was frequently cited as a reason for early discontinuation, it was not reported as severe. Based on time to first report of the event, the frequency of patients reporting acne declines after the first 6 months, suggesting that use over longer periods of time will not increase the proportion of patients with acne.

In other studies of DHEA in SLE, acne as been consistently the most commonly reported adverse event felt to be associated with treatment. In the Taiwan study, acne was reported in almost 60% of patients receiving GL701; however, in that study acne was also reported at a much higher rate, almost 30%, in the placebo group. Since the proportion of patients receiving concomitant corticosteroids was much higher in the Taiwan study, this may explain the higher rates of acne in both treatment and placebo groups.

Hirsutism, although less frequent than acne, seemed to be more specifically associated with GL701, reported in approximately 14% of GL701 patients, compared to only 2% in placebo patients. Based on

time to first reporting of this advent, the frequency of hirsutism also appeared to decline over time. In the Taiwan study, hirsutism was not reported in either treatment group, suggesting a possible racial difference in occurrence or in reporting of this adverse event.

7.4.2 Hypertension

Hypertension, reported as an adverse event, was significantly more frequent in the GL701 200 mg group than placebo, but the numbers of reports of hypertension was small, 20 (7.9%) in GL701 200 mg patients compared to 7 (2.7%) in placebo patients. The apparent imbalance arises mainly from the adverse events reported in Study GL94-01, where 8 GL701 200 mg patients had an AE of hypertension reported, compared to none in the placebo group. At the request of the FDA, hypertension was further analyzed by creating a composite AE of HYPERTENSION. This composite AE consisted of patients (1) experiencing new onset hypertension, (2) experiencing an increase in hypertension, or (3) requiring an additional anti-hypertensive medication or an increase in dose of existing anti-hypertensive medications. Additionally, analysis of baseline (pre-existing) hypertension was requested.

Briefly, these were defined as follows:

- New onset hypertension was a patient without previous history of hypertension who experienced one or more of the following: a new AE of hypertension, new treatment for hypertension, or an increase in blood pressure score on the SLAM from normal at baseline, diastolic BP < 90 (SLAM score = 0), to elevated BP (SLAM score of 1 or greater).

- An increase in hypertension was a patient with a previous history of hypertension who experienced either or both of a new AE of hypertension or increase in SLAM BP score from baseline.

- Requiring additional anti-hypertensive medication or increase in dose was a patient with a previous history of hypertension who required an additional medication or increased dose of pre-existing anti-hypertensive medication. Patients who only switched from one medication to another were not included.

Hypertension at baseline or pre-existing hypertension was defined as any patient with at least one of the following: hypertension in the medical history, an adverse event of hypertension with an onset date before study drug was stared, prior use of an anti-hypertensive medication where the indication was listed as hypertension, or a diastolic BP $\geq$ 90 at baseline.

As seen in the table below, overall, the proportion of patients with this composite adverse event, HYPERTENSION, appears well balanced between placebo and GL701 200 mg in both GL94-01 and GL95-02. There also does not appear to be an imbalance in the subcategories with the exception that in Study GL94-01, there were more GL701 patients than placebo who met the criteria of "increase in dose of or additional anti-hypertensive medication." This finding is likely due to the fact that there were substantially more patients at risk (i.e., those with pre-existing hypertension) in both the GL701 100 mg and 200 mg groups compared to the placebo group. Not shown in **Table 7-23**, there was a baseline imbalance of pre-existing hypertension in GL94-01: 22 (34.4%) of 64 placebo, 23 (36.5%) of 63 GL701 100 mg and 34 (53.1%) of 64 GL701 200 mg. This baseline imbalance was not noted in Study GL95-02, and the proportion of patients with increase in dose of or additional anti-hypertensive is similar for both placebo and GL701 200 mg in GL95-02.

Table 7-23: Patients with Composite AE of HYPERTENSION

Study GL94-01			
	Placebo (N=64)	**100 mg (N=63)**	**200 mg (N=64)**
Composite HYPERTENSION	22 (34.4%)	17 (27.0%)	24 (37.5%)
New Onset of Hypertension	11 (17.2%)	11 (17.5%)	11 (17.2%)
Increase in Hypertension	11 (17.2%)	2 (3.2%)	10 (15.6%)
Increase in dose of or additional Anti-Hypertensive medication	0	4 (6.3%)	3 (4.7%)
Study GL95-02			
	Placebo (N=192)		**200 mg (N=189)**
Composite HYPERTENSION	27 (14.1%)		22 (11.6%)
New Onset of Hypertension	8 (4.2%)		8 (4.2%)
Increase in Hypertension	8 (4.2%)		6 (3.2%)
Increase in dose of or additional Anti-Hypertensive medication	11 (5.7%)		8 (4.2%)

The above analyses suggest that the higher proportion of patients with hypertension reported as an adverse event, 7 placebo patients vs 20 GL701 200 mg patients, does not necessarily reflect a actual differences in patients with increased blood pressure. When further measures of increased blood pressure are included in a "composite" adverse event of hypertension, there appears to be no difference between the treatment groups.

More importantly, whatever the explanations for a difference between placebo and GL701 in number of adverse events reported as hypertension, this difference appears unlikely to reflect an increase in clinically significant hypertension. Severe hypertension was noted in only one patient, and hypertension was not cited as a reason for discontinuing study drug in any patient. Additionally, association with worsening renal function was noted in only 2 GL701 200 mg patients and 1 GL701 100 mg patient, as well as 1 placebo patient. This suggests that these adverse events of hypertension, whatever their mechanism or explanation, were neither a cause nor a result of worsening renal function in SLE patients.

7.4.3 Abdominal Pain

The number of patients with adverse events reported under the COSTART term of "pain abdomen" (abdominal pain) was approximately the same in the placebo and GL701 200 mg groups. However, there appeared to be an imbalance in one study, GL94-01, where abdominal pain was more frequent in GL701 patients, reported in 6.3%, 11.1% and 21.9% of placebo, GL701 100 mg and GL701 200 mg patients, respectively (N=4, 7, and 14). The majority of events were mild and transient in nature and were not deemed by the investigator as related to study drug. The patterns of complaints for all three treatment groups were nonspecific and did not differ from one another. The complaints did not suggest either involvement of one type of organ or permanent organ damage.

In Study GL95-02, abdominal pain was reported with the same frequency in both treatment groups: 15.6% of placebo and 14.3% of GL701 treated patients. The overall prevalence and types of complaints were similar between the two treatment groups. Similar to Study GL94-01, the majority of events were mild in intensity, transient, and did not require intervention. The pattern of complaints for the two treatment groups was nonspecific and again did not suggest involvement of any one organ or permanent organ damage.

However, although the number of patients in both studies reporting abdominal pain characterized as "severe" in intensity was small, there was an imbalance between GL701 and placebo. No patient in the placebo group, 2 (3.2%) of the GL701 100 mg group, and 6 (2.4%) of the GL701 200 mg group reported severe abdominal pain. Because of this imbalance, patients with severe abdominal pain were investigated further.

With the exception of two cases of appendicitis (GL701 100 and 200 mg, respectively), all the other cases of severe abdominal pain resolved and did not appear to be related to study drug.

Most importantly, 7 of the 8 patients completed the study; only one patient (GL701 200 mg) withdrew early, due to menstrual irregularities. Six of the 8 patients with severe abdominal pain elected to participate in the open-label GL95-01 study and all 6 completed the study without recurrence of symptoms of abdominal pain.

Thus, the pattern of these adverse events of severe abdominal pain does not suggests a specific common etiology, nor relationship to SLE or to study drug.

7.4.3.1 Increase in Serum Creatinine

In the pooled data from the two double-blind studies, GL94-01 and GL95-02, 0 of 256 patients in the placebo group had creatinine increase reported as an adverse event, 1 of 63 GL701 100 mg (1.6%), while 6 of 253 patients (2.4%) in the GL701 200 mg group had this adverse event, p=0.015, placebo vs. GL701 200 mg.

Although there was an imbalance in the few patients with creatinine increase reported as an adverse event, overall serum creatinine did not increase in any of the three treatment groups (placebo, GL701 100 mg or GL701 200 mg), as judged by a mean or median increase in serum creatinine, and also there was no difference in change in creatinine between the three groups. Nevertheless, this imbalance between GL701 200 mg and placebo of patients with creatinine increase reported as adverse events warrants further exploration.

All adverse events were reviewed to determine if there were any other events that might imply an increase in serum creatinine. Five additional events were identified: a GL701 patient as “reduction in creatinine clearance” reported as an adverse event; a placebo patient with “ATN” reported as an adverse event; a placebo patient with “renal flare” reported as an adverse event; a GL701 patient with “renal failure” reported as an adverse event; and a GL701 patient with “renal insufficiency” reported as an adverse event.

Additionally, patients who had a serum creatinine increase from baseline to last visit of $\geq$ 0.3 mg/dl were identified. There were 13 such patients, 4 (1.6%) in the placebo group, 3 (4.8%) in the GL701 100 mg group, and 6 (2.4%) in the GL701 200 mg group. Five of these 13 patients also had an adverse event suggesting decreased renal function, and so are included in the group described above.

Thus, there were a total of 21 patients with either a serum creatinine increase at last visit of at least 0.3 mg/dl, or an adverse event suggesting decreased renal function, with 5 of these patients meeting both criteria. These patients were reviewed in greater detail in order to determine if hematuria, decrease in C3, increases in 24-hour urine protein, or immunosuppressive therapy for lupus nephritis were present as

well. The findings from these 21 patients are described more fully in the tablular summary below (**Table 7-24**).

Table 7-24: Summary of Patients with Serum Creatinine Increase or Adverse Events Related to Creatinine Change

Patient ID	Study Drug	AE Verbatim Term	Meaningful increase[1] in serum creatinine	Baseline creatinine mg/dl	Creatinine at time of AE	Creatinine at last on-treatment visit	Meaningful increase[2] in 24-hour urine protein	New Hematuria[3]	C3 normal to low[4]	Comment
18141	placebo	Acute tubular necrosis	Yes	1.1	1.5	1.5	--	--	--	ATN at time of hospitalization for pneumonia. Patient removed from study.
20511	placebo	--	Yes	1.1	--	1.5	--	--	--	Azathioprine added for proliferative glomerulonephritis.
21626	placebo	--	Yes	1.2	--	1.5	--	--	--	
48813	placebo	--	Yes	1.0	--	1.5	--	--	--	
27205	200 mg GL701	Creatinine increased	Yes	1.3	1.7	1.9	--	--	--	Proteinuria and hematuria at baseline.
19454	200 mg GL701	Creatinine increased	Yes	1.3	1.6	2.5	--	--	--	Proteinuria at baseline which increased on treatment
19454	200 mg GL701	Creatinine increased, RBC in urine	Yes	1.3	1.9	1.9	Yes	Yes	--	
20436	200 mg GL701	--	Yes	1.6	--	2.0	--	--	--	
35654	200 mg GL701	--	Yes	0.9	--	1.5	--	--	--	
36640	200 mg GL701	--	Yes	4.2	--	5.2	--	--	Yes	
27323	100 mg GL701	Creatinine increased	Yes	1.9	1.9	2.5	--	--	--	Proteinuria and hematuria at baseline
30265	100 mg GL701	--	Yes	1.1	--	3.0	Yes	Yes	--	Cyclophosphamide added following discontinuation of study drug.

Table 7-24: Summary of Patients with Serum Creatinine Increase or Adverse Events Related to Creatinine Change (cont.)

Patient ID	Study Drug	AE Verbatim Term	Meaningful increase[1] in serum creatinine	Baseline creatinine mg/dl	Creatinine at time of AE	Creatinine at last on-treatment visit	Meaningful increase[2] in 24-hour urine protein	New Hematuria[3]	C3 normal to low[4]	Comment
30268	100 mg GL701	--	Yes	1	--	2.4	Yes	Yes	Yes	Cyclophosphamide added following discontinuation of study drug.
18717	placebo	Renal flare	No	0.7	0.8	0.9	--	--	--	Proteinuria at baseline
3152	200 mg GL701	Renal insufficien -cy	No	1.1	Not recorded	1.2	--	--	--	"Renal insufficiency" during acute GI bleed secondary to NSAIDs.
36514	200 mg GL701	Renal failure	No	1.6	Not recorded	1.8	--	--	--	Hospitalized for renal failure, prednisone increased, cyclophosphamide added
38758	200 mg GL701	Creatinine increased	No	1.3	1.5	1.5	--	--	--	Proteinuria at baseline
38781	200 mg GL701	Creatinine increased	No	1.7	1.7	1.7	--	--	--	
38800	200 mg GL701	Creatinine increased	No	1.7 at screen 1.3 at qualifying visits	1.4	1.4	--	--	--	
41440	200 mg GL701	Creatinine increased	No	1.3	1.6	1.5	--	--	--	
43554	200 mg GL701	Decrease in creatinine clearance	No	1.2	1.3	1.3	--	--	--	Cr Cl decreased from 85 to 41/ml/min/1.73m^2, but may have been due to inadequate urinary collection

1. Serum creatinine at last visit 0.3 mg/dl greater than baseline.
2. Increase in urine protein > 500 mg/24 hours over baseline, or approximate doubling or more of baseline if baseline > 1000 mg/24 hours.
3. No hematuria at baseline, but hematuria ($\geq$ 5 RBC/hpf) at last visit.
4. C3 normal at baseline, but low (< 85 mg/dl) at last visit.

Review of these 21 patients demonstrates that 8 (the last 8 patients in the table with no "meaningful increase in serum creatinine") had an adverse event whose verbatim term suggested decreased creatinine clearance, but did not have a meaningful increase in serum creatinine. Only one of the eight, a GL701 200 mg patient, appeared to have experienced significant renal dysfunction. She was hospitalized for renal failure and received immunosuppressive therapy. The remaining 7 did not have confirmatory evidence of meaningful changes in urinary protein, new hematuria or intervention for renal SLE.

Of the 13 patients whose serum creatinine did increase by the end of study (≥ 0.3 mg/dl over baseline), 4 were placebo patients and 9 GL701 patients. Only 7 had associated findings such as new medications for renal lupus, increased proteinuria, hematuria or decreased complement. Such findings were present in 2 of the 4 placebo patients, and were present in 5 of the 9 GL701 patients.

Taken as a whole, these findings suggest renal dysfunction, as identified by increased serum creatinine, was quite uncommon, and generally not related to the findings of increased proteinuria, new onset hematuria or decreased C3.

7.4.3.2 Proteinuria

There was a higher mean change from baseline for 24 urinary protein with GL701: the mean change was 44.9 mg/24 hours for placebo, and 324.9 mg/24 hours and 329.4 mg/24 hours for the GL701 100 mg and 200 mg groups, respectively. Because the 24 hour urinary protein excretion data is skewed, median values may be more appropriate. The median changes were 4.0 mg/24 hours, 69.0 mg/24 hours, and 23.0 mg/24 hours respectively. These median changes still suggested higher urinary protein excretion associated with GL701.

In order to further understand the significance of patients with increases in 24-hour urine protein, additional analyses of this parameter protein excretion were conducted. For the purpose of this analysis, a meaningful increase in proteinuria was defined as an absolute increase of greater than or over 500 mg at last visit compared to baseline, or a doubling of 24 hour protein excretion if baseline was over 1000 mg/24 hours comparing baseline and last visit data. However, examination of the individual patients with increases in proteinuria revealed 3 patients with large increases that approached, but did not quite meet, the criterion of doubling. These three patients were a placebo patient with pitting edema whose proteinuria increased from 2743 mg to 4700

mg/24 hours, and 2 GL701 200 mg patients whose proteinuria increased from 2420 mg to 4648 mg/24 hours, and 1319 mg to 2574 mg/24 hours respectively.

Twenty-five (25) patients meeting these criteria from the two placebo-controlled were identified, including the 3 patients described above who approached, but did not quite meet, the criterion of doubling. As a percent of all randomized patients, these were 8 (3.1%) of 256 placebo patients, 6 (9.5%) of 63 GL701 100 mg patients, and 11 (4.3%) of 253 GL701 200 mg patients.

Of these 25 patients, only 1, a placebo patient had a normal 24 hour protein excretion (< 150 mg/24 hours) at baseline. Among the 24 patients with proteinuria at baseline, a meaningful increase in proteinuria, as defined above, occurred in 7 (5.6%) of 126 placebo patients, 6 (14.0%) of 43 GL701 100 mg patients, and 11 (7.8%) 141 GL701 200 mg patients.

Of the 135 patients receiving GL701 100 mg or 200 mg who did not have proteinuria at baseline, none had a meaningful (> 500 mg/24 hours) increase over baseline in proteinuria.

To understand the possible clinical significance of the increase in proteinuria, each of these 25 patients was reviewed for associated changes in serum creatinine, adverse events suggesting renal impairment, or immunosuppressive therapy required for lupus nephritis. In this analysis, the proportion of patients is similar within the treatment groups. Of the 25 patients, 4 placebo patients, 1 GL701 100 mg patient, and 6 GL701 200 mg patients had increased proteinuria which may have been associated with clinically significant renal dysfunction. These 11 patients are briefly described in **Appendix 8**.

The remaining 14 patients with increased proteinuria, 4 placebo, 5 GL701 100 mg and 5 GL701 200 mg, did not appear to have significant renal events, changes in renal function, or significant medication changes

In summary, analysis of the 25 individuals who had what appeared to be meaningful increases in 24-hour urine protein at the last visit (an increase of 500 mg/24 hours over baseline if baseline less than 1000 mg/24 hours; or a doubling, or close to doubling, of baseline at last visit, if the baseline was $\geq$ 1000 mg/24 hours) revealed a slightly higher proportion of such patients in the GL701 200 mg group compared to placebo; and even a higher rate in the GL701 100 mg group. However, the number of such patients was relatively low, and all but one, a placebo patient, had pre-existing proteinuria. No GL701 patient without proteinuria at baseline had a meaningful increase (>500 mg) over baseline in proteinuria at the last visit.

In only 11 of these 25 patients did the increase in proteinuria appear to be associated with medically or clinically significant renal dysfunction, as judged by adverse events, changes in medication, or changes in renal function. Expressed as a proportion of patients with pre-existing proteinuria, these are 3.2% of 126 placebo, 2.3% of 43 GL701 100 mg, and 4.3% of 141 GL701 200 mg patients. Thus, less than 5% of patients with pre-existing proteinuria in any of the treatment groups demonstrated a meaningful increase in proteinuria.

7.4.3.3 Hematuria

Hematuria was reported as an adverse event in 1 placebo, 2 GL701 100 mg and 9 GL701 200 mg patients. However, in 4 of these 12 patients (1 placebo patient and 3 GL701 200 mg patients), this adverse event appeared to be related to menses, vaginal bleeding or urinary tract infection. None of these 4 patients had red blood cells (RBCs) in the urine at their last visit.

In an additional 4 patients, although the adverse event was termed "hematuria", there did not appear to be a meaningful change in red blood cells in the urine. Also, these patients did not have associated meaningful increases in 24-hour urine protein (as defined **in Section 7.4.3.2 Proteinuria**), increase in serum creatinine (increase of at least 0.3 mg/dl from baseline to last visit), adverse events suggesting other renal involvement, or new use of immunosuppressives.

The remaining four patients had significant hematuria. Two of these, both GL701 200 mg patients, had significant hematuria without associated renal findings, and two, a GL701 100 mg and a GL701 200 mg patient, had significant hematuria as well as increases in serum creatinine. Thus, of the 12 patients with hematuria reported as an adverse, only two appeared to have any evidence of other renal dysfunction.

Another way of examining hematuria is to analyze patients whose RBCs in the urine were normal at baseline and increased (>5/hpf) at end of treatment. Forty-eight (48) patients were identified. These were 15 (5.9%) of 256 placebo patients, 5 (7.9%) of 63 GL701 100 mg patients, and 28 (11.1%) of 253 GL701 200 mg patients. When these 48 patients are examined for the occurrence of renal involvement, as judged by meaningful increases in 24 urinary protein excretion at end of treatment (as defined **in Section 7.4.3.2 Proteinuria**), increases in serum creatinine at end of treatment ($\geq$ 0.3 mg/dl increase from baseline to last visit), or renal adverse events, only 12 patients, 5 of the placebo patients, 2 of the GL701 100 mg patients, and 5 of the GL701 200 mg patients met one or more of these criteria. Only five of these patients (2 placebo, 1 GL701 100

mg, and 2 GL701 200 mg) required immunsuppressive or other specific therapy for renal SLE patients.

In conclusion, although there were more GL701 patients with new hematuria as determined from a “shift” table, when these patients are examined in detail, there does not appear to be a difference between placebo and GL701 for new hematuria accompanied by SLE renal involvement, as manifested by changes in urinary protein excretion, increased creatinine, or new therapy for renal SLE.

7.4.4 Decreases in Serum Complement

Mean values of C3 and C4 decreased in both treatment groups during the placebo-controlled trials, but the mean decrease was larger in the GL701 group. Similar findings were noted in the Taiwan study and also for placebo-treated patients who received GL701 for the first time in Study GL95-01.

While C3 reduction was common, most placebo and GL701 treated patients remained within the normal range for either C3 or C4. For example, 16% of patients treated with GL701 at 200mg/day went from normal to low C3 (<85 mg/dl) level at their final visit compared with 6% of placebo-treated patients.

The significance of these changes in C3 were further explored by determining whether patients whose C3 declined from normal also had evidence of renal involvement.

Two of 14 placebo patients with a decrease in serum C3 from normal to low at end of study also had new onset of hematuria (defined as normal urine RBC at baseline, and > 5RBC/hpf at last visit).

In the GL701 200 mg group, of the 36 patients who had a decrease in C3 from normal to low, only 3 had new onset hematuria, 2 had meaningful increase in proteinuria (as defined **in Section 7.4.3.2 Proteinuria**), and 2 had increased creatinine (serum creatinine increased at least 0.3 mg/dl from baseline to last visit). In the GL701 100 mg group, 1 of 9 with a decrease in C3 also had an increase in creatinine. Importantly, none of the placebo or GL701 patients with a decrease of C3 from normal to low received immunosuppressive therapy. Thus, although there were a number of patients whose C3 declined on study, only a very small number, less than 3% of any treatment group, also had some evidence of SLE-associated changes in renal function, suggesting that decreased C3 in this study was neither a sign nor a cause of worsening SLE renal involment.

The mechanism of decreased C3 apparently caused by GL701 is not known. Although increased consumption of C3 because of increased disease activity is one possibility, the clinical improvement and lack of association with worsening renal disease seen in the placebo-controlled trials are not consistent with such a mechanism. While an abnormally low level of complement often is a manifestation of disease in SLE, it is not considered a good predictor of disease flare, and the clinical significance of decreases in C3 is not clear. In one study, decreased C3 was predictive only for vasculitic flares, "although the confidence intervals were wide" (Esdaile, 1996).

Another possible mechanism is that C3 decreased due to decreased production of C3 in the GL701 treated patients. C3 is an acute-phase reactant which increases during the acute-phase response (Juan, 1993). During improvement or stabilization of disease activity, as observed in the GL701 clinical trials, C3 might be expected to decline. In addition, androgens may decrease hepatic synthesis of a number of proteins synthesized in the liver. The decrease in SHBG levels noted in the GL701 patients is consistent with decreased hepatic protein synthesis, as is the recent observation that testosterone treatment of patients with Klinefelter's syndrome decreases serum complement substantially, without evidence of any manifestations of autoimmunity (Yesilova, 2000).

The pro-inflammatory cytokine IL-6, which is elevated in active SLE (Reuss-Borst, 2000), is known to stimulate hepatic secretion of C3 (Nonogaki, 1995; Zhao, 2000). Although IL-6 levels were not measured in the GL701 clinical trials, DHEA has been reported to reduce macrophage production of IL-6 (Straub, 1998; Padgett and Loria, 1998), and it is possible that the observed reductions in C3 reflect GL701-induced suppression of IL-6.

In summary, although GL701 caused an increased number of patients (in comparison to placebo) to have a decrease in C3, the decline in C3 was not associated with renal dysfunction, suggesting the effect may be mediated by a reduction in complement synthesis rather than an enhancement of consumption. Furthermore, information from the medical literature suggests that a decline in serum complement may be a direct effect of suppression of complement production by androgens.

7.4.5 Serum Lipids

Decreases in lipids, particularly HDL-C and triglycerides, were consistently seen in studies of GL701. Pooled data from the placebo-controlled studies demonstrated that administration of

GL701 resulted in a predictable decline in serum lipids within three months of study drug initiation. The reduction was most evident for HDL-C and triglycerides, less so for total cholesterol and minimal for LDL cholesterol. When placebo patients entered the open-label study GL95-01, and switched to GL701, a decrease in lipids occurred, again within three months. By contrast, when GL701 patients entered the open-label study, continuing to receive GL701, generally no further decrease in lipids occurred with the possible exception of a small further decrease in triglycerides. Taken as a whole, these findings suggest that administration of GL701 consistently causes an early, but not progressive decrease in serum lipids, primarily HDL-C and triglycerides.

In general, as is well known, decreased in HDL-cholesterol levels are believed to be associated with risk of greater cardiovascular events, while decreased triglycerides are believed to decrease cardiovascular events. Current guidelines (NCEP: NIH, 1994) call for serum HDL-C to be maintained ≥ 35 mg/dl. Based on these guidelines, approximately 17% of patients in the GL701 200 mg went from normal to low (< 35 mg/dl), compared to 7% in the placebo group.

The mechanism of the decrease in HDL-cholesterol and triglycerides caused by GL701 is not known. Usually there is an inverse correlation between changes in HDL-C and triglycerides (Lamarche, 1999). However, in GL701-treated patients the reduction in HDL-C was accompanied by a reduction, rather than the expected increase in serum triglycerides. Lowering of HDL-C and triglycerides have previously been described in post-menopausal women receiving combination estrogen/androgen treatment (Watts, 1995).

The mechanism by which androgenic hormones, including DHEA, reduce triglyceride and HDL-C levels is unknown, but may relate to increased hepatic lipase activity (Haffner, 1983, Kantor, 1985), and increased HDL-C flux and excretion (Haffner, 1983; Hazzard, 1984). The HDL particle is important in the process of “reverse cholesterol transport” whereby cholesterol is removed from peripheral tissues, incorporated into the HDL particle (HDL-C), and transported to the liver for breakdown and excretion in the bile. If this is the mechanism, the observed decreases in HDL-C and triglycerides may reflect increased removal of cholesterol from peripheral tissues via enhanced HDL-C clearance, rather than decreased production of HDL-C.

The above-described proposed mechanism for decreased triglycerides and HDL-cholesterol associated with GL701 and other androgens would suggest that the reduction in HDL-C observed with GL701 may not necessarily signify an increased risk of atherosclerosis. However, whatever

the mechanism for decreased HDL-cholesterol, it would be prudent to follow NCEP guidelines while monitoring lipids in patients receiving GL701.

7.4.6 Effects of GL701 on Sex Hormones

7.4.6.1 Increases in Testosterone Levels

The changes in hormones observed in GL701 patients are consistent with the role of DHEA as a precursor to sex steroids, and particularly androgenic hormones. In the placebo-controlled trials, testosterone was increased in a dose related manner in SLE patients, both pre- and post-menopausal, receiving GL701; and androgenic adverse events such as acne and hirsutism showed an increased frequency, as did lipid changes usually associated with administration of androgens. There were similar findings in Taiwanese patients (GBL96-01). Increased levels of testosterone were also noted both in healthy pre-menopausal volunteers (Study GL96-02) and healthy post-menopausal volunteers (Study GL99-01).

In the placebo-controlled trials, only 33 (18.5%) of GL701 200 mg patients and 1 (1.7%) of GL701 100 mg patients exceeded upper limit of normal for testosterone. SHBG was reduced approximately 40% in the GL701 group. Since testosterone binding to SHBG is approximately 66% (Dunn, 1981), the androgenic effects observed in these trials may also be a result of increased availability of free testosterone, greater than would be anticipated from the serum levels.

In non-pregnant women, the most serious risks associated with increased levels of testosterone would be virilization, i.e., evidence of irreversible androgenic changes such as deepening of the voice, androgenic alopecia, or clitoral hypertrophy. Such events were not reported in the GL701 clinical trials. However, the long-term risks of the increased testosterone levels caused by GL701 are not yet known.

There are only preliminary studies of GL701 in men with SLE, and use in men at this time is not recommended. Nevertheless, if administered to men, the most serious risks of increased testosterone would be initiation or promotion of hormone dependent tumors, particularly carcinoma of the prostate. Although hormone data from the still blinded pilot study in men with SLE have not been analyzed, published studies have shown that the administration of DHEA to men with decreased pituititary function will increase testosterone levels (Young, 1997). The effect of DHEA administration on testosterone levels in healthy men is less clear. Chronic

administration of DHEA to healthy elderly men was shown to increase testosterone levels (Wolf, 1998), but less information is available for healthy young men. Whether GL701-induced increased levels of testosterone would be of sufficient magnitude to increase the risk of initiation or promotion of prostate cancer over the risk already present from endogenous levels of testosterone in men is entirely unknown at this time. There has been a single report of apparent worsening of a pre-existing cancer of the prostate in a patient who was taking DHEA as a nutritional supplement (Jones, 1997).

7.4.6.2 Increases in Estradiol Levels

Changes in estradiol were less consistent than with testosterone. Overall, in pre-menopausal healthy women volunteers or pre-menopausal women with SLE, it appeared that GL701 was not associated with meaningful increases in estradiol.

In post-menopausal patients with SLE receiving GL701, there appeared to be a modest increase in estradiol levels, but these data were confounded by inclusion of some clearly peri-menopausal patients. However, this increase was still evident among post-menopausal women not on HRT, whose baseline estradiol levels were < 25 pg/ml. The increase was similar or lower than that usually associated with standard hormone replacement therapy. Furthermore, an increased frequency of adverse events related to estrogenic effects, such as meno-metrorrhagia, thrombotic events, or weight gain was not noted in either pre- or post-menopausal groups. Specifically, if GL701 had a consistent estrogenic effect, spontaneous vaginal bleeding, associated with an estrogenic effect, should have been much more frequent in the post-menopausal patients receiving GL701. In the placebo-controlled studies, only 7 (6%) women on GL701 reported menorrhagia, metrorrhagia or vaginal hemorrhage compared with 2 (2%) post-menopausal women treated with placebo. By contrast, in the Post-menopausal Estrogen/Progestin Interventions (PEPI) Trial, 66.4% of 119 women taking estrogen only had at least one unscheduled endometrial biopsy for spontaneous bleeding compared to 13.6% taking cyclic medroxyprogesterone acetate. (The Writing Group for the PEPI Trial, 1996)

The only estrogenic effects noted in the placebo-controlled studies were increased bone density (which may have been an androgenic, rather than estrogenic effect), and decreased FSH and LH in post-menopausal women. Since estradiol is only approximately 37% bound to SHBG (Dunn, 1981), in contrast to testosterone, the impact of decreased SHBG is less likely to have a substantial effect on estrogenic activity.

A. Possible Effects on Hormone-Dependent Tissues

Any increase in estrogen levels in post-menopausal women, however, raises the theoretical concern of increased risk of estrogen-associated malignancies in the target population. Two malignancies that are potentially related to estrogen are of special concern: breast cancer and endometrial cancer. In January 1999, the protocols for Study GL95-02 and the open-label extension study (Study GL95-01) were amended to include mammography and uterine ultrasonography for post-menopausal patients.

As of January 31, 2001 results of mammography are available from 49 patients, 5 who received only placebo and 44 who received GL701. Some of these 44 had received placebo in the placebo-controlled studies, but then received GL701 in the open-label extension study. All of these mammagraphies have either been normal or had benign findings. To date, one of these mammographies has resulted in breast biopsy. That biopsy was negative for breast cancer.

Including patients who participated in the placebo-controlled and open-label extensions studies, four patients, three GL701 and one placebo, were reported to have developed breast cancer, either while receiving study drug or up to 15 months following study completion. These four patients are summarized in the **Table 7-25** below. One of these patients received only placebo, while one received placebo followed by GL701 (in the open-label extension study), and the other two received GL701 only. All 4 were in the post-menopausal age group, though three, were classified as pre-menopausal, still reporting active menses, and had not received HRT. The fourth patient, age 61, was post-menopausal. She had received Premarin/Provera HRT for approximately 10 years.

Table 7-25: Patients with Breast Cancer

Patient ID	Study Drug	Age at Dx	Duration of GL701 Treatment	Menopausal Status	Dx On/Off Study	HRT	Comment
12013	GL701 200 mg	49	730 days	Pre (active menses)	Off (4 mos)	No	Well differentiated infiltrating ductal carcinorma. Had taken birth control pills for four years in the past.
18035	GL701 200 mg	48	362 days	Pre (active menses)	Off (15 mos)	No	Invasive ductal carcinoma Received cytotoxic therapy prior to diagnosis Remote family history of breast cancer

Patient ID	Study Drug	Age at Dx	Duration of GL701 Treatment	Menopausal Status	Dx On/Off Study	HRT	Comment
38480	Placebo	45	0 days	Pre (active menses)	On study	No	Infiltrating lobular carcinoma
45006	GL701 200 mg	61	455 days	Post	On study	Yes	Infiltrating ductal carcinoma. Premarin/Provera, since 1989

Expressed as a percent of patients, 1 (1.3%) of 77 control patients (patients receiving only placebo) developed breast cancer, compared to 3 (0.6%) of 495 patients who received GL701 at any time (either during the double-blind studies, or placebo followed by GL701 during open-label extension, or GL701 in both double-blind and open-label phases). Although three of the patients were pre-menopausal and actively having menses, their ages were 45, 48, and 49 years. Expressed as a percentage of patients 45 years or older, these rates are 1 (4.2%) of 24 control or placebo patients (i.e., patients who never received GL701), and 3 (1.5%) of 206 GL701 patients (i.e, patients who received GL701 in any study).

A more relevant way of expressing the breast cancer rate may be in terms of cancers per years of "observation". Patients were, of course, followed closely and systematically while on study. The only systematic observation following study was a 6 week follow-up assessment in GL95-02, a three to five month follow-up in GL94-01, and three months in GL95-01. However, two of the breast cancers were reported by investigators following completion of study and following the protocol specified follow-up: 4 and 15 months after the end of treatment. In order to estimate time of observation for the study population, it is necessary to assume that any other case of breast cancer would have also been reported spontaneously, even after patients completed the study and required followup. It is not unreasonable that breast cancer would be reported well beyond the defined follow-up period, though it is possible that there have been other cases of breast cancer in patients who participated in these trials not reported to the Sponsor. These assumptions are subject to the possibility of ascertainment bias, but there is no obvious reason to expect that development of breast cancer would have differential reporting between GL701 and placebo.

Under the assumptions described above, patient-years of observation for each GL701 patient were calculated from the time of the patient's first exposure to GL701, either in the double-blind studies, or in the open-label study, to March 1, 2000 (the date the last breast cancer was reported). For placebo patients, patient-years of observation for each placebo patient, were calculated from first exposure to placebo in the double-blind studies to March 1, 2000, for those placebo patients who never received GL701, or for those switched to GL701 in open-label study, to the time of entry into the open-label study.

The rates of breast cancer per patient-year of observation were similar for placebo and GL701. These were estimated to be 1.8 per 1000 women-years of observation for GL701, and 2.3 per 1000 women-years for placebo. Expressed as a rate per patient year of observation for patients 45 years or older, these rates are 4.6 per 1000 for GL701 and 6.5/1000 for placebo.

These rates also appear similar to background or control rates in several recent publications investigating risk of breast cancer. In a recently published cohort study of HRT, those subjects not receiving any form of HRT had a breast cancer rate of approximately 3.9/1000 women-years of observation (Schairer, 2000). This rate is similar to the rates described above for GL701 or placebo in women 45 years or older. It is of interest that the rate was only slightly higher in those receiving unopposed ("estrogen-only") HRT, relative risk of 1.1 (4.4/1000 women years), compared to those without HRT. For those women receiving some form of estrogen combined with progestins, the relative risk was even higher, 1.2 or 1.3, depending on whether progestin was administered continuously or intermittently.

In the Nurses' Health Study (Colditz, 1995), the relative risk of breast cancer with or without estrogen use increased with age in post-menopausal women. In addition, duration of estrogen therapy was a key factor, with little incremental risk attributed to treatment of less than 5 years' duration. The Breast Cancer Prevention Trial (Fisher, 1998) followed 13,388 women over the age of 35, randomly assigned to receive Tamoxifen or placebo, for 69 months. In the control group, the cumulative incidence of breast cancer was 43.4 cases per 1000, or 7.5 cases/1000 women per year. This incidence compares favorably with the limited data described above from the studies of GL701, although the patients in this trial were enrolled because of higher risk of breast cancer. This may mean that they had a higher intrinsic risk of breast cancer than the population participating the GL701 studies, although SLE patients are thought also to have a higher rate of cancer, including breast cancer (Ramsey-Goldman, 1999).

Taking this data as a whole, it would appear that increased risk, if any, of breast cancer associated with GL701 therapy should be low. GL701 therapy produces estradiol levels that are lower or similar to HRT. GL701 therapy is not accompanied by progestin therapy. The data from the GL701 clinical trials so far do not suggest an increased rate of breast cancer. As noted by Willett (2000), any increased breast cancer risk associated with estrogen therapy without progesterone is low, especially with short-term (2 to 3 years) use, and declines rapidly with cessation of use. Nevertheless, in view of the limited data and relatively short duration of exposure to GL701 compared with the large studies of breast cancer risk with estrogen administration in post-menopausal women, it would appear prudent for post-menopausal patients receiving GL701 to follow the current mammography guidelines for post-menopausal women.

By contrast to breast cancer, administration of exogenous estrogens unopposed by progestins appears to cause a substantial increase in risk of cancer of the endometrium. When estrogen is administered to post-menopausal women it causes proliferation of the endometrium. When this proliferation is unopposed by progestin, it can result in hyperplasia in as many as 20% of patients (which is reversible when the estrogen is stopped). The risk of endometrial cancer appears related to the dose of estrogen, and may be increased 5 to 10-fold (PEPI 1996; Lindsay, 1996; Persson, 1999; Beral, 1999). Whether testosterone or other androgens can oppose this proliferation is not known, but DHEA has been reported to be stimulatory to the vaginal epithelium while being inhibitory to the endometrium (Labrie, 1997; Sourla, 1998) at circulating levels comparable to those reported in the GL701 pharmacokinetic studies. Labrie (1997) administered DHEA as a 10% cream to 14 post-menopausal women for 12 months. Circulating levels of DHEA achieved at 12 months in these women increased 10-fold from baseline (baseline 3.9 nmol/l [0.11 μg/dl] to 31.2 nmol/l [0.90 μg/dl]). An estrogenic effect on the vagina, as shown by vaginal maturation indices, was observed while biopsies demonstrated the endometrium remained atrophic in all women.

It would appear less likely that GL701 has effects on the endometrium as had been described for unopposed HRT. As described above, systemic estrogenic effects were not noted in the clinical studies. Specifically, rates of meno-metrorrhagia and vaginal bleeding in GL701 treated patients did not suggest a substantial impact on the uterus. Certainly, the rate of these events was far lower than reported in the PEPI trial. Published studies of DHEA in other areas also do not suggest a consistent effect on the endometrium.

Twenty-four post-menopausal women treated with GL701 have had uterine ultrasound screening for endometrial hyperplasia. Twenty-one of these patients had exposure to GL701 for at least 6 months. Endometrial hyperplasia was not detected in any of them including three patients who had uterine biopsies. By contrast, in the PEPI study, approximately 20% of women receiving unopposed estrogens for one year demonstrated endometrial hyperplasia. Based on the PEPI study, the magnitude of increased risk with GL701, if any, of endometrial hyperplasia and endometrial carcinoma appears low in relation to the risk in women receiving unopposed estrogen therapy.

In summary, with respect to any increased risk of endometrial carcinoma associated with GL701, placebo-controlled trials, showed that administration of GL701 caused a modest increase in estradiol levels in post-menopausal women, but there were no clear systemic estrogenic effects, including effects on the uterus, as judged by adverse events, changes in serum chemistries, and limited uterine ultrasound studies. Nevertheless, the long-term consequences of prolonged exposure to GL701, as with any hormone therapy including well-established therapies such as hormone replacement therapy, are not yet fully known.

7.5 SPECIAL POPULATIONS

7.5.1 Race

In the GL701 placebo-controlled studies, racial differences in patterns of adverse events or clinical laboratory findings were not observed with the possible exception that acne was reported less frequently by African American patients, in approximately 26%, compared to approximately 36% in Caucasian patients. The significance of this finding is unknown. In the Taiwan study where the patients were all of Chinese extraction, hirsutism was not reported as an adverse event, unlike the studies in the United States. This may indicate a decreased racial susceptibility to hirsutism related to androgens.

7.5.2 Age, Sex, and Menopausal Status

There were very few patients older than 65, and no patients under 18, to allow meaningful comparisons of safety by age.

Adverse event rates and clinical laboratory findings were analyzed by treatment and menopausal status. There appeared to be no meaningful treatment related differences by menopausal status, other than the hormone related findings described above.

SLE occurs mostly (approximately 90%) in women. The scientific rationale for the efficacy and safety of DHEA in SLE is predominantly based on findings that DHEA levels are reduced in women with SLE. Studies in a murine model of SLE suggest administration of DHEA or other androgens improves SLE in female mice, and that castration worsens SLE in male mice. Results of one preliminary study in male lupus suggested that some androgens cause worsening of SLE (Lahita, 1992). These considerations would preclude pooling men and women in the same study. Consequently, the development of GL701 has been predominantly in women, with only an ongoing pilot study in men. Therefore the safety conclusions in this NDA are based only studies in women. The safety of GL701 in men with SLE remains to be established with additional studies.

7.5.3 Pregnancy

Although patients participating in the clinical studies were to be on effective birth control methods, eight women became pregnant during clinical trials of GL701. Four (3 on GL701 and 1 on placebo) delivered normal babies at term, and four (3 on GL701 and one on placebo) had therapeutic termination of pregnancy. No evidence of teratogenic effect or alteration in urogenital tract was reported.

Despite its widespread use as a nutritional supplement, there are little data on DHEA kinetics during human pregnancy and no reports of its use in pregnancy.

Segment I, II, and II reproductive studies have shown no adverse effects on fertility nor evidence of teratogenicity, but embryotoxicity and fetoxicity were seen in pregnant rats administered GL701 in doses of 15 mg/kg.

With the limited human data and given the known estrogenic and androgenic pharmacologic activity of DHEA, it is appropriate to restrict the labeling for GL701 as it relates to its use in pregnant women.

7.5.4 Drug Interactions

Since the goal of Study GL94-01 was to demonstrate reduction in corticosteroid dose while maintaining constant or improved activity of the patients' SLE, a multi-dose interaction study of GL701 and prednisone was conducted in healthy female volunteers. The goal of the study (GL96-02) was to investigate whether GL701 could affect the bioavailability and pharmacokinetics of orally administered prednisone. The study demonstrated that there was no pharmacokinetic interaction, confirming that any effect of GL701 on corticosteroid reduction was not based on altering the bioavailability, pharmacokinetics, or pharmacodynamics of prednisone.

Other than the above-described study, formal drug interaction studies have not been performed with GL701. When used to treat SLE, it is likely to be used concurrently with two other agents that may affect lipid metabolism: antimalarials and glucocorticoids.

In the clinical trials conducted to support the NDA, approximately 33% of women were taking hydroxychloroquine. In Study GL94-01 all women were required to be taking glucocorticoids, and in studies GL95-01 and GL95-02 glucocorticoid use was permitted; approximately 58% of women enrolled in GL95-02 were using glucocorticoids at baseline.

7.5.5 Potential Interaction with Hydroxychloroquine for Serum Lipids

Hydroxychloroquine has been reported to decrease LDL-C and total cholesterol (Hodis, 1993). In some studies, hydoxycholoroquine appeared to lower HDL (Hodis, 1993; Mendez, 1999) while in others it was reported to increase HDL (Borba & Bonfa, 1999). Likewise, in some studies, hydroxychloroquine decreased triglycerides (Borba & Bonfa, 1999; Hodis, 1993) while other studies reported no effect on triglycerides (Olga, 1999*)*.

In order to determine whether there was an interaction between the effects of hydroxychloroquine and of GL701 on serum lipids, mean change from baseline for serum lipids was analyzed by treatment group and by use of antimalarials at baseline. The data was pooled by treatment group from the placebo-controlled studies. Since patients were not stratified by baseline use of antimalarials, and since many of the patients were also on corticosteroids which may also affect serum lipids, there are limitations to interpretation of this type of analysis.

As shown in **Table 7-26** below, for the GL701 group, the major finding appeared to be that triglycerides were further decreased in patients receiving antimalarials along with GL701, compared to GL701 patients not receiving antimalarials. In the placebo group, triglycerides

increased on study, but there was a smaller increase in placebo patients receiving antimalarials. For the other lipids, no clear trend is seen that would suggest a possible interaction.

Table 7-26: Effects of Antimalarials on Serum Lipids (GL94-01 and GL95-02)

	Mean (Median) Change from Baseline to Last On-Treatment Visit				
		HDL-Cholesterol	**LDL-Cholesterol**	**Total Cholesterol**	**Triglycerides**
Antimalarials at Baseline	Placebo N=78	-3.2 (-3.0)	-5.6 (-5.0)	-8.0 (-6.0)	6.0 (4.5)
	GL701 N*=68 to 69	-8.9 (-10.0)	-1.3 (-2.0)	-15.0 (-13.0)	-29.1 (-23.0)
No Antimalarials at Baseline	Placebo N*=158 to160	-1.3 (-1.0)	-1.5 (-3.0)	-1.8 (-3.0)	11.5 (11.5)
	GL701 N*=156 to 158	-8.4 (-8.0)	-3.7 (-5.0)	-11.7 (-15.0)	-6.3 (-13.0)

*Number of patients varies slightly by test.

Thus, the addition of GL701 to a regimen that contains hydroxychloroquine appears to not to have substantial impact on the effect of antimalarials on serum lipids, with the possible exception of increasing the magnitude of a decrease in triglycerides.

7.6 RELATIONSHIP OF DOSE TO SAFETY

The results of GL94-01 where two doses of GL701, 100 mg/day and 200 mg/day, were compared to placebo provide the only information regarding dose response. In that study, there was a clear pharmacokinetic dose relationship. If downstream hormones such as testosterone and estradiol are considered evidence of pharmacodynamic activity, there was also clear evidence of a pharmacodynamic dose relationship.

Serum levels of DHEA-S, estradiol, and testosterone were increased in the GL701 200 mg group compared to the 100 mg group, which were in turn increased over the levels in the placebo group. Changes in cholesterol, HDL-C, LDL-C showed small, possibly dose related, differences between the 100 mg and 200 mg groups, but changes in triglycerides were not at all dose related. A dose relationship was not seen for other clinical laboratory values. Likewise, adverse events also did not show a dose relationship. For example, the two most common adverse events that seemed related to GL701, acne and hirsutism, showed no dose relationship whatsoever. Acne was reported in 44.4% of the 100 mg group, 43.8% of the 200 mg group, but in 18.8% of the placebo group. Similarly, hirsutism was reported in 11.1% of the 100 mg group, 7.8% in the 200 mg, but in 4.7% of the placebo group.

One possible explanation for the lack of relationship to dose (at least in the dose range of 100 to 200 mg) would be that for cutaneous androgenic effects such as acne and hirsutism, only a threshold dose is required for those susceptible to that effect; and that higher doses may not cause more patients to become susceptible to that effect. The findings by Barry (1998) would be consistent with this. In that ascending dose study in SLE, they found that the frequency of acne was not related either to dose of DHEA or to serum levels of DHEA or DHEA-S. In addition, patients who had not developed dose limiting acne at doses of 50 to 100 mg/day did not necessarily develop it as the dose was increased progressively to as high as 600 mg/day.

8 BENEFIT/RISK ASSESSMENT

8.1 BENEFIT

GL701 is intended as treatment for women with mild to moderate, active SLE, a disease for which the few treatment options available all have substantial toxicity and limited efficacy.

Current therapies for active SLE are limited and include only hydroxychloroquine, corticosteroids, and immunosuppressive/cytotoxic drugs. Patients are exposed to multiple toxicities, many serious, during treatment with these drugs. Since patients are often dependent on steroids and immunosuppressive drugs, discontinuing them or reducing their dose may cause serious flares, while continued use leads to multiple cumulative toxicities. Reduction of corticosteroid use is especially important for SLE patients, as complications of high dose or chronic use of corticosteroids account for much of the morbidity that develops in SLE including infection, osteonecrosis, osteoporosis, atherosclerotic vascular disease, myopathy, and diabetes. The immunosuppressive/cytotoxic agents frequently used in SLE such as cyclophosphamide, azathioprine and methotrexate also cause increased risk of infection, bone marrow suppression, sterility, bladder toxicity, cirrhosis, and malignancy. Hydoxychloroquine is also used in SLE although it has a limited effect and is associated with rare but serious retinal toxicity.

The benefits of GL701 in the treatment of SLE were demonstrated in two double-blind, placebo-controlled, randomized clinical trials in the US, and are supported by findings from a double-blind placebo-controlled trial in Taiwan and early Phase I/II studies conducted at Stanford University. These included improved manifestations of SLE, reduction of steroid requirements, fewer flares, improvement of patient's overall self-assessment of the status of her SLE, and improvement in bone mineral density.

In the GL94-01, GL701 was clinically and statistically superior to placebo in achieving sustained reduction of daily corticosteroid doses. This effect approached significance in all randomized patients, and was significant for those with active SLE, baseline SLEDAI > 2. A dose response relationship was also noted, with GL701 200 mg having a higher response rate compared to GL701 100 mg. In patients with baseline SLEDAI > 2, the mean and median number of days patients' daily prednisone dose (or its corticosteroid equivalent) was $\leq$ 7.5 mg were significantly greater in the GL701 200 mg treatment group than placebo.

In a second study, GL95-02, the signs and symptoms of SLE were clinically and statistically improved in GL701-treated patients in comparison to placebo patients. This improvement was demonstrated in several ways including: a) increase in the proportion of patients who were responders (i.e., had stabilization or improvement of their SLE); b) a decrease in flares; c) improvement in well being as measured by the Patient VAS; and d) prevention of loss of bone mineral density during steroid therapy. Additionally, the proportion of patients experiencing certain manifestations of SLE reported as adverse events, such as mucosal ulcers, alopecia, and myalgia were decreased in the GL701 group.

In a placebo-controlled study with a similar design to GL95-02 conducted in Taiwan, improvement in SLE was further confirmed. In that study, GL701-treated patients had significantly fewer flares and showed significantly greater improvement in well being as measured by patient VAS, compared to the placebo patients. Likewise, in a placebo-controlled phase II study at Stanford University, compared to placebo, DHEA-treated patients had fewer flares and showed improvement in overall well being, as measured by Patient VAS. The DHEA-treated patients were also shown to be able to reduce their corticosteroid dose.

Thus, improvement in GL701-treated patients has been demonstrated in all three domains in SLE. Reduction in manifestations of SLE or improvement in the area of SLE disease activity was demonstrated by the increase in proportion of responders and decrease in proportion of patients with flares. Achievement of sustained reduction of corticosteroids in corticosteroid-dependent patients, without worsening of disease, as well as improvement in bone mineral density in patients receiving corticosteroids chronically, are important benefits for the domain of SLE damage. A benefit in the patients' overall assessment of quality of life or constitutional symptoms was demonstrated by improvement in the Patient VAS.

8.2 RISKS

In studies of more than 600 women, including 242 treated with GL701 for more than one year, and 36 treated for more than two years, no serious immediate risks were seen. From these studies, the safety profile of GL701 appeared almost entirely predictable from its androgenic, and to a lesser extent, estrogenic effects. In all double-blind studies and an open-label extension study, androgenic adverse events (as reflected in acne and hirsutism) were the most common events associated with GL701. Almost all complaints of acne and hirsutism were deemed by the

investigators as mild or moderate, none was serious and only a small number of patients terminated from the studies prematurely due to these complaints.

The adverse events described above do not appear to pose significant patient risk. They represent part of the safety profile of GL701, but are not events potentially related to significant organ damage, likely to lead to hospitalization, or otherwise meet the definition of a serious adverse event. Most importantly, such events are generally reversible with treatment and/or cessation of GL701 treatment, allowing the patient to make her own informed decision about whether the discomfort associated with these events or their treatment balances the benefit being experienced.

The clinical laboratory changes associated with GL701 generally were also directly related to its pharmacology as a precursor of sex steroids. There were no clinical laboratory changes associated with GL701 suggesting acute or chronic significant organ damage. In comparison to patients receiving placebo, these were predictable but non-progressive decreases in: serum total cholesterol, HDL-C and triglycerides; decreases in C3; and increases in androgen and estrogen levels. However, the changes in lipids and sex hormones, while not causing significant acute or chronic toxicity during the clinical studies, have potential or theoretical long-term risks of increased atherosclerosis and hormone dependent malignancies. Although not observed during clinical trials, these potential risks have to be considered as part of the safety profile of GL701.

Decreased HDL-C has been linked by epidemiological studies to increased risk of cardiovascular events secondary to atherosclerosis, though such studies suggest that is partially offset by lower levels of triglycerides. The mechanism of this increased risk of atherosclerosis is generally thought to be reduced cholesterol transport and excretion due to lowered HDL-C. These epidemiological studies, however, do not address the cause of the decreased HDL-C in the populations surveyed. In addition, there is pre-clinical evidence that androgens, including DHEA, may lower HDL-C by increasing cholesterol flux and excretion and, if so, the observed lowered levels of HDL-C with GL701 may not necessarily reflect increased risk of atherosclerosis.

Nevertheless, until there is sufficient epidemiological data concerning cardiovascular risk associated with GL701 in women with SLE, the possibility that long term treatment with GL701 increases the risk of atherosclerosis will have to be balanced against improvements in SLE. In the absence of additional information, this unknown risk can be best managed and minimized by

following the guidelines of the National Cholesterol Education Program (NCEP, 1994) with respect to cholesterol and cardiovascular risk management.

Decreased levels of C3 were observed in GL701-treated SLE patients. While the mechanism of reduced C3 in SLE is generally thought to be due to consumption during antigen-antibody complex-induced inflammation, such as in renal glomeruli or other sites, there is contraversy whether low C3 levels corrolate with disease activity. When the patients who experienced decrease in C3 in the double-blind studies were examined in detail, there appeared to be no association with signs of renal involvement by SLE or increased renal dysfunction. Furthermore, there is evidence suggesting that androgens may lower C3 by decreasing hepatic production of C3, rather than causing consumption due to increased inflammation. Additional laboratory studies currently ongoing may help elucidate whether C3 was decreased due increased consumption or decreased production.

Although GL701 has been well-tolerated in studies with up to 2 years of exposure, there are potential concerns relating to any elevations of androgenic and estrogenic steroid hormones. There was no evidence of virilization, including deepening of the voice, androgenic alopecia, or clitoral hypertrophy reported in GL701 clinical trials in women with SLE.

In pre-menopausal women, it appeared that GL701 patients demonstrated small increases in estradiol. Adverse events potentially related to these increased hormone levels, such as meno-metrorrhagia, thrombotic events or weight gain, did not appear increased in GL701-treated pre-menopausal (or post-menopausal) patients.

In post-menopausal SLE patients not receiving HRT in the double-blind studies, there also appeared to be a variable increase in estradiol levels, but lower or similar to those that would be achieved by standard HRT. For those women already receiving HRT, there appeared to be only a small increase in estradiol levels over the levels from the HRT. Any increase in estrogen levels in post-menopausal women, however, raises the theoretical concern of increased risk of estrogen-associated malignancies in the target population. Two malignancies that are related to estrogen are of special concern: breast cancer and endometrial cancer.

There were 3 (1.5%) cases of breast cancer in 206 GL701 patients older than 45 years and 1 (4.2%) case in 24 placebo patients of the same age group who never received GL701. Expressed as a rate per patient-year of observation for patients 45 years or older, these rates are 4.6/1000 for GL701 and 6.5/1000 for placebo. These are similar to breast cancer rates reported for post-

menopausal women. However, in view of the limited data and relatively short duration of exposure to GL701 compared with the large studies of breast cancer risk with estrogen administration in post-menopausal women, it would appear prudent for post-menopausal patients receiving GL701 to follow the current mammography guidelines for post-menopausal women.

By contrast to breast cancer, administration of exogenous estrogens unopposed by progestins appear to cause a substantial increase in risk of cancer of the endometrium. When estrogen is administered to post-menopausal women it causes proliferation of the endometrium. When this proliferation is unopposed by progestin, it can result in hyperplasia in as many as 20% of patients (which is reversible when the estrogen is stopped). The risk of endometrial cancer appears related to the dose of estrogen, and may be increased 5 to 10-fold. It is not known whether the effects of GL701 on the endometrium are similar to estrogen, though in other studies DHEA administration was shown not to cause endometrial proliferation. In the GL701 clinical trials, an increased rate of estrogenic effects such as meno-metrorrhagia and vaginal bleeding were not noted in GL701 patients. In addition, uterine ultrasound screening and uterine biopsies have not shown endometrial hyperplasia in post-menopausal GL701 patients. The lack of finding of endometrial hyperplasia associated with GL701 may be related to relatively small increases in estradiol levels and/or modification of any effects of increased estradiol by the androgenic effects of GL701. Based on comparisons with findings in post-menopausal women receiving unopposed estrogens, the magnitude of increased risk, if any, of endometrial hyperplasia and endometrial carcinoma appear to be low.

In summary, the significant risks associated with GL701 are largely, if not entirely, the theoretical risks of increased atherosclerosis and hormone dependent tumors. These should be evaluated in relation to the benefits of improvement in SLE provided by GL701, and in relation to the considerable morbidity from SLE itself, as well as the very limited therapeutic options available to women with SLE. These options include corticosteroids and immunosuppressive agents which have substantial and already well-established (not theoretical) toxicities.

In addition, any potential risks associated with GL701 should be evaluated in the context of the current availability of DHEA as a dietary supplement. In this context, patients taking DHEA as a dietary supplement are receiving it in a form that is essentially unregulated. As such, any patient taking DHEA as a dietary supplement is receiving a potent hormone of uncertain and inconsistent quality, purity, dose, and without the benefit of labelled information concerning proper dosing or warnings about common and uncommon risks.

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