SL0008, 2007-002589-37

CLINICAL STUDY REPORT SYNOPSIS

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This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

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Sponsor:

UCB, Inc.

1950 Lake Park Drive

Smyrna, GA 30080

USA

Official study title:

A Phase 2b, multicenter, open-label, follow-up study to assess the safety and efficacy of epratuzumab in serologically-positive systemic lupus erythematosus patients with active disease who participated in study SL0007

CLINICAL STUDY REPORT SYNOPSIS: SL0008

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Name of finished product: Epratuzumab	**Volume:** Not applicable	
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Title of study: A Phase 2b, multicenter, open-label, follow-up study to assess the safety and efficacy of epratuzumab in serologically-positive systemic lupus erythematosus patients with active disease who participated in study SL0007

Investigator(s): This was a multicenter study; 44 investigators enrolled a total of 203 subjects.

Study site(s): This was a multicenter study; 44 sites in 11 countries enrolled subjects.

Publication(s) (reference[s]): None

Studied period: 3 years and 7 months **First subject enrolled:** 05 May 2008 **Last subject completed:** 28 Dec 2011	**Phase of development:** Phase 2b

Objective(s): The primary objective of this study was to continue to assess the safety of epratuzumab dosed at 1200mg biweekly, for a total of 2 doses in 12-week retreatment cycles, in moderate to severe systemic lupus erythematosus (SLE) subjects. The secondary objectives of the study were to continue to assess the tolerability and efficacy of epratuzumab, the kinetics and attributes of B and T cells in circulation, the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of epratuzumab, the health-related quality of life (HRQoL) benefits of epratuzumab treatment, and the utility benefits of epratuzumab treatment.

Methodology: This was a Phase 2b, multicenter, open-label, follow-up study to SL0007 that was designed to assess the safety and efficacy of epratuzumab in serologically-positive SLE subjects with active disease. Subjects were treated with epratuzumab 1200mg every other week (QOW) infusions in 12-week treatment cycles. Each 12-week cycle consisted of 2 biweekly dosing visits, followed by evaluation visits (no study drug administered) at Week 4 and Week 8, and then the cycle repeated at Week 12. The 12-week cycles continued for the duration of the study.

Subjects returned for evaluations of SLE disease activity and usage of SLE medications (steroids, immunosuppressants, antimalarials, etc) every 4 weeks beginning 4 weeks after the first infusion of the first treatment cycle and continuing throughout the study until the last study visit. It was intended that SL0008 would continue until the approval of a local marketing application for the indication of SLE; however, the study was stopped early for logistical reasons (to consolidate the Phase 2 and Phase 3 open-label extension studies). Subjects who completed SL0008 had the option to enroll in the Phase 3, long-term, extension study, SL0012, and receive continued epratuzumab treatment. The end of the study (SL0008) was defined as the final subject's last visit.

Safety data collected during this study were reviewed periodically by an independent data safety monitoring board. No safety concerns were identified during SL0008, and the independent data safety monitoring board (DSMB) supported the continuation of the study throughout.

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An independent central reader group was employed to read the BILAG assessments that were performed by the investigators.

Number of subjects (planned and analyzed): Approximately 175 subjects were planned to participate in this study. A total of 203 subjects were enrolled into the study who had participated in a 12-week, double-blind, placebo (PBO)-controlled, dose- and dose regimen-ranging study to determine the safety and efficacy of epratuzumab in serologically positive SLE subjects with moderate or severe disease (SL0007). All 203 subjects were included in the Safety Population.

Diagnosis and main criteria for inclusion: The study included male and female serologically-positive SLE patients with active disease who participated in study SL0007. The subjects must have completed Week 12 of SL0007 or were early terminating at Week 8 (Visit 8) or later due to treatment failure as described in the SL0007 protocol. In addition, subjects who completed SL0007 must have maintained eligibility requirements (including concomitant medication restrictions) throughout their participation in the SL0007 study. Subjects who terminated SL0007 early due to use of restricted concomitant lupus medications (eg, increased corticosteroid dose) resulting in treatment failure may have been eligible to enter SL0008.

Subjects must not have had active, severe neuropsychiatric SLE or active severe SLE disease activity which involved the renal system. Subjects must not have exhibited evidence of an immunosuppressive state, had a history of chronic infection, malignant cancer, or antiphospholipid antibody syndrome, received any live vaccines or prohibited medications during the study, or had significant hematologic abnormalities not attributed to lupus.

Test product, dose(s) and mode of administration, batch number(s): The test article was epratuzumab at a concentration of 10mg/mL prepared in vials for slow iv infusion using only phosphate-buffered saline as a vehicle/buffer for the infusion procedure. Subjects received epratuzumab 1200mg infusions in 12-week treatment cycles. Subjects were premedicated with diphenyhydramine 25mg to 50mg by mouth (po) or intravenously (iv) and acetaminophen 500mg to 1000mg po 30 to 60 minutes prior to infusion in order to minimize infusion reactions.

The following batch numbers of study drug were administered to the subjects during SL0008: [redacted]

Duration of treatment: Subjects received epratuzumab 1200mg infusions in 12-week treatment cycles for the duration of the study. Each 12-week cycle consisted of 2 biweekly dosing visits. The duration of the study (up to 3.5 years) was determined by the date that the study was terminated by the sponsor, and the last subject had completed the study.

Reference therapy, dose(s) and mode of administration, batch number(s): None; all subjects received epratuzumab 1200mg infusions during the study.

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Criteria for evaluation:

Efficacy: The main efficacy variable was the number and percentage of subjects with British Isles Lupus Assessment Group (BILAG) improvement, which was defined as BILAG As at study Baseline (SL0007 Visit 1) improved to B/C/D and BILAG Bs at study Baseline (SL0007 Visit 1) improved to C/D and no BILAG worsening in other BILAG organ systems, such that there were no new BILAG As or 2 new BILAG Bs as compared to Visit 1 of SL0007.

Other efficacy variables included the following:

1. A combined index response variable evaluated at every 4 weeks through Week 48 and then every 12 weeks through completion/withdrawal, incorporating the following criteria for achievement of responder status (ie, all criteria must have been met to achieve/maintain responder status):
   - (BILAG Landmark Analysis) BILAG improvement, defined as BILAG As at Baseline (SL0007 Visit 1) improved to B/C/D and BILAG Bs at study Baseline (SL0007 Visit 1) improved to C/D and no BILAG worsening in other BILAG organ systems such that there were no new BILAG As or 2 new BILAG Bs; and
   - No worsening in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) compared to study Baseline (SL0007 Visit 1); and
   - No worsening in physician's global visual analog scale (VAS) assessment of disease activity ('no worsening' defined as less than 10% worsening) compared to SL0007 Visit 1; and
   - Subjects who were treatment failures could not be responders.
2. The combined index responder analysis above including an additional criteria of "stabilization or improvement" of the 36-Item Short Form Health Survey (SF-36) response, measured at 12-week intervals.
3. BILAG scores summarized by conversion of A/B/C/D/E to a numeric value of 12/8/1/0/0, respectively (ie, "Total BILAG"), measured at 4-week intervals through Week 48 and then at 12-week intervals.
4. SLEDAI assessment score measured at 4-week intervals through Week 48 and then at 12-week intervals.
5. Patient and physician global disease assessment score (physician's global assessment of disease activity [PGA] and patient's global assessment of disease activity [PtGA] from 10cm VAS) measured at 4-week intervals through Week 48 and then at 12-week intervals.
6. Percentage of subjects achieving SF-36 "stabilization or improvement" (defined as no changes more negative than -0.8 in physical component summary (PCS) or >-2.5 changes in any of the 8 domain scores) as compared to Baseline (SL0007 Visit 1), measured at 12-week intervals.
7. SF-36 PCS and mental component summary (MCS), measured at 12-week intervals.

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8. European Quality of Life-5 Dimensions (EQ-5D) measured at 12-week intervals.
9. Proportion of subjects meeting treatment failure.
10. Total daily steroid dose measured at 4-week intervals.
11. Time to severe flare (defined as a new BILAG level A disease in 1 body system or BILAG level B disease in more than 1 body system) for subjects who entered the study without severe flare as defined by BILAG.
12. Time to moderate or severe flare (defined as a new BILAG level B disease in 1 body system or severe flare) for subjects who entered the study without moderate or severe flare as defined by BILAG.
13. SLEDAI responder (≥4-point improvement over Baseline of SL0007).
14. Time to sustained response (at 2 consecutive visits) for subjects entering the study with flare as defined as 1 BILAG A or 2 BILAG Bs or a SLEDAI of ≥6. As measured by the following:
    - BILAG index improvement
    - Combined index response variable.
15. Time to withdrawal due to lack of efficacy.
16. Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) assessment score measured at Week 12 and then at 24-week intervals for the remainder of the study.

Pharmacokinetics/pharmacodynamics: The PK profile and immunogenicity of epratuzumab was characterized. Blood samples to determine the plasma concentrations of epratuzumab were drawn from all subjects once at nondosing visits, twice at each dosing visit (1 predose and one 30 minutes [±10 minutes] postdose) for the duration of the study.

B and T cell flow cytometry assessments were conducted to assess the time course of changes to B and T cells in circulation following drug exposure as well as the attributes (eg, maturity) of cells present posttreatment compared to pretreatment. B and T cell studies were taken at the first dosing visit of each treatment cycle and at 4 weeks post first dose of each treatment cycle.

Immunological: Autoantibodies and other lupus-related laboratory parameters were assessed from blood samples taken at Week 0 and 8 weeks post first dose of each subsequent dosing cycle to assess their relationship to prognosis and treatment response. These antibodies were also assessed at early termination (ET).

- Antinuclear antibody (ANA)
- Antibodies to extractable nuclear antigen (anti-ENA)

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- Smith antibody (anti-Sm)
- Ribonucleoprotein antibody (anti-RNP)
- Double-stranded deoxyribonucleic acid antibody (anti-dsDNA)

Immunoglobulins (immunoglobulin G [IgG], immunoglobulin M [IgM], and immunoglobulin A [IgA]), B cells (CD19-positive cells), and T cells (CD3-positive cells) were determined from blood samples taken at the first dosing visit of each treatment cycle and 4 weeks post first dose of each treatment cycle. These parameters were also assessed at ET.

The following potential lupus-associated laboratory parameters were determined in blood samples taken at Week 0 and 8 weeks post first dose of each subsequent treatment cycle:

- Complement 3 (C3)
- Lupus anticoagulant (LAC)
- C-reactive protein (CRP)
- Anticardiolipin
- Rheumatoid factor (RF)

Anti-epratuzumab antibody concentrations (human anti-human antibody [HAHA]) were determined from plasma samples taken at the first dosing visit of each treatment cycle and 4 weeks post first dose of each treatment cycle.

Safety: Safety variables included assessments of adverse events (AEs; including infusion reactions); clinical laboratory evaluations (hematology, serum chemistry, and urinalysis); vital sign measurements (diastolic and systolic blood pressure, temperature, pulse rate, and respiration rate) and weight; physical examination; and immunoglobulin production.

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Statistical methods:

Efficacy analyses: All statistical analyses used descriptive and exploratory methods. In general, summary statistics (arithmetic mean, standard deviation [SD], median, minimum, and maximum) for quantitative variables and frequency tables for qualitative data were presented. Summaries of concentration data were based on geometric mean and geometric SD as well as arithmetic versions. Each summary table was supported by a subject data listing, and each figure was supported by a summary table.

Relative day accompanied visit dates, sample dates, onset/start dates, and resolution/stop dates in subject data listings. In case of partial date, relative day was computed based on an imputed whole date, but the reported partial date should have been displayed in the listing.

Unless otherwise stated, derived variables were computed to the maximum level of decimal precision without rounding. Rounding normally occurred after computation of descriptive statistics of the variable across all subjects to a reasonable level of precision.

Unless otherwise indicated, 'Baseline value' referred to the last value obtained prior to first infusion obtained in the preceding study, SL0007, and followed the analysis conventions employed for SL0007. The 'Visit 1 value' referred to the value from the Screening Visit in SL0008.

For vital signs (blood pressure, pulse rate, respiration rate, and temperature) measured on the days at which an infusion occurred, an infusion-specific Baseline was used, defined as the value obtained just prior to infusion of study drug.

The statistical analysis focused on the Safety Population for subject disposition, as well as all efficacy and safety analyses, and the PK Population was used for summaries of epratuzumab plasma concentrations. The Safety Population consisted of all subjects who were administered at least 1 dose (including a partial dose) of study drug. The PK Population consisted of all subjects who were administered study drug and had at least 1 epratuzumab plasma concentration measurement.

The BILAG improvement rate was based on BILAG data only. The number and percentage of subjects meeting BILAG improvement criteria was summarized by visit. BILAG improvement was defined as BILAG As at Baseline improved to B/C/D and BILAG Bs at Baseline improved to C/D and no BILAG worsening in other BILAG organ systems, such that there were no new BILAG As or 2 new BILAG Bs as compared to Visit 1 of SL0007.

Subjects who dropped out were classified as nonresponders at all subsequent visits.

The BILAG improvement rate was also summarized by SL0007 treatment group using the following categories:

- PBO
- Epratuzumab 1200mg QOW
- Epratuzumab 600mg every week (QW)
- All active doses (including epratuzumab 600mg and epratuzumab 1200mg)
- Overall

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Summary and conclusions:

Subject disposition: During SL0008, 203 subjects were enrolled who had participated in a 12-week, double-blind, PBO-controlled, dose- and dose regimen-ranging study to determine the safety and efficacy of epratuzumab in serologically positive SLE subjects with moderate or severe disease (SL0007). At study entry for SL0008, 17.2% of subjects had received PBO in the prior double-blind study (SL0007), and 17.7%, 15.8%, 16.7%, 18.2%, and 14.3% of subjects had received epratuzumab doses of 100mg QOW, 400mg QOW, 1200mg QOW, 1800mg QOW, and 600mg QW, respectively. The mean number of days subjects participated in SL0008 was 692.6 days, with a range of 29 to 1191 days.

A total of 203 subjects were enrolled, treated, and included in the Safety Population. Of these 203 subjects, 55.7% of subjects completed the study. A subject was considered as having completed the study based on the investigator's response on the study termination case report form (CRF) page (ie, completed vs prematurely discontinued). The most common reasons for discontinuation were AE (14.3%), withdrew consent (12.3%), and lack of efficacy (11.3%).

Efficacy results: For the main efficacy variable of BILAG improvement, the percentage of subjects with BILAG improvement from Baseline increased over time in the All Subjects group (range: 34.5% to 63.8% at time points for which there were at least 25 evaluable subjects); however, the actual number of subjects with BILAG improvement was relatively similar over time through Year 3, Week 12, and this increase in rate may be due to a reduction in the denominator as subjects left the study and may not have met BILAG improvement criteria. The observed increase in the All Subjects group was maintained beyond the end of Year 2 (58.2% at Visit 41, Year 3, Week 24), but was decreased at the last visit (48.3%). The increasing trend in BILAG improvement over time was observed in subjects previously treated with epratuzumab (all doses) and for those treated with PBO. The percentage of subjects with BILAG improvement was notably higher for the SL0007 epratuzumab 600mg QW group compared with the SL0007 epratuzumab 1200mg QOW group at all visits, including Screening. Compared across groups, the largest degree of improvement was observed for subjects previously treated with PBO.

The percentage of subjects with BILAG improvement showed a general trend toward increasing over time for white, black, and Asian subjects. In general, the percentage of subjects with BILAG improvement was highest in Asian subjects and lowest in black subjects across ethnic groups; however, meaningful comparisons among ethnic groups cannot be made due to the small number of Asian (N=22, 10.8%) and black (N=20; 9.9%) subjects in the study population.

The percentage of subjects with BILAG improvement from Baseline ranged from 18.2% to 57.1% for subjects with a renal BILAG score of A/B at Baseline for the first year of the study; the percentage of subjects with BILAG improvement increased from that of Year 1 at later time points. Subjects with a renal BILAG score of A were not to be enrolled in the study (per exclusion criterion 2); however, 1 subject with a renal BILAG score of A was enrolled and was included in this analysis. Meaningful comparisons by renal BILAG score cannot be made due to the small number of subjects with a renal BILAG score of A/B.

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Treatment response

For the observed case analysis (ie, with no imputation), the percentage of subjects with treatment response from Baseline increased over time in the All Subjects group. However, the actual number of subjects with treatment response was relatively similar over time through the end of Year 2, and this increase in rate may be due to a reduction in the denominator as subjects left the study and may not have met treatment response criteria. The observed increased in the All Subjects group was maintained beyond the end of Year 2, but was decreased at the last visit. The increasing trend in treatment response was observed in subjects previously treated with epratuzumab (all doses) and for those treated with PBO. The percentage of subjects with a treatment response was slightly higher for the SL0007 epratuzumab 600mg QW group compared with the SL0007 epratuzumab 1200mg QOW group at most visits, including Screening. The largest degree of improvement was observed for subjects previously treated with PBO.

Treatment response and SF-36 stabilization or improvement

To understand whether the addition of a subject-reported measure supported the responder definition, in addition to meeting all of combined treatment response criteria, subjects also had to achieve SF-36 "stabilization or improvement" (defined as no changes more negative than -0.8 in PCS or >-2.5 changes in any of the 8 domain scores) as well as not to use prohibited medications during the SL0008 in order to be classified as a responder.

The program has evolved since the protocol for SL0008 was written, and the name of this endpoint has been changed to "stabilization or lack of deterioration" in the ongoing Phase 3 studies to be in agreement with the thresholds used as they are cited in the literature.

The percentages of these responders ranged from 12.9% to 20.8% for all subjects and were generally consistent over time. The percentage of subjects meeting the responder criteria was notably lower across all doses compared with treatment response because of the addition of the medication and SF-36 components to the criteria.

BILAG total score

Mean change in BILAG total scores decreased (ie, improved) from Baseline throughout the SL0008 treatment period. A mean decrease from Baseline was observed at Visit 1/Screening of SL0008 (-10.3 points) and decreased further with repeated treatment to Visit 25 (Year 2, Week 24; -17.1 points), then was maintained for the duration of the study. The mean BILAG total score was decreased by approximately 60% compared to Baseline with long-term use of epratuzumab. In addition, the mean total BILAG score was decreased by approximately 50% compared to Baseline at the last visit.

SLEDAI total score

Mean change in SLEDAI total scores decreased (ie, improved) from Baseline throughout the SL0008 treatment period. A mean decrease from Baseline was observed at Visit 1/Screening of SL0008 (-4.0 points) and decreased further with repeated treatment to Visit 29 (Year 2, Week 36; -7.9 points),

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then was maintained for the duration of the study. The mean SLEDAI total score was decreased by approximately 50% compared to Baseline with long-term use of epratuzumab. In addition, the mean SLEDAI score was decreased by approximately 40% compared to Baseline at the last visit.

SLEDAI improvement

At all time points, nearly 90% of subjects had no worsening in their SLEDAI score throughout the study. During the treatment period of SL0008, the percentage of subjects with at least 4-, 6-, or 8-point improvement in SLEDAI total score increased or was maintained throughout the SL0008 treatment period. Approximately two-thirds of the subjects maintained a 6-point improvement with long-term epratuzumab treatment, and approximately 50% of subjects maintained an 8-point improvement with long-term epratuzumab treatment. At the last visit, 85.7% of subjects achieved no worsening, 67.5% of subjects achieved a 4-point improvement, 51.2% achieved a 6-point improvement, and 39.7% of subjects achieved an 8-point improvement.

Of the SLEDAI components that were present in subjects at Baseline, the percentage of subjects with lupus headache, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, inflammatory type rash, alopecia, mucosal ulcers, pleurisy, pericarditis, and fever decreased with repeated epratuzumab treatment, indicating improvement in these components.

PGA and PtGA

Observed mean PGA scores ranged from 21.0 points to 49.5 points from Baseline through Visit 41, Year 3, Week 24. Observed mean PGA scores decreased from Baseline. For change from Baseline, a mean decrease of approximately 30% was observed at Visit 1/Screening of SL0008 (-14.8 points) that decreased further with repeated treatment to Visit 29 (Year 2, Week 36; -28.5 points) and was then generally maintained for the duration of the study. At the last visit, the decrease in the mean PGA score was 20.4 points, which was consistent with mean decreases observed throughout the study.

The majority of subjects had no worsening at all time points during the SL0008 treatment period (range: 93.9% to 100.0%). At the last visit, 89.7% of subjects had no worsening during SL0008.

Similar trends were observed for mean PtGA scores and the percentage of subjects with no worsening in PtGA scores during SL0008. Observed mean PtGA scores ranged from 32.2 points to 51.4 points from Baseline through Visit 41, Year 3, Week 24.

In general, physicians reported greater improvements in disease activity than the subjects themselves.

SF-36 scores and SF-36 stabilization

Mean SF-36 domain, PCS, and MCS scores increased from Baseline during the treatment period in SL0008 and were generally maintained through the end of treatment in SL0008. Changes from Baseline in the median SF-36 domain, PCS, and MCS scores were positive and exceeded the minimal clinically important difference (MCID), implying improved quality of life.

A slightly greater improvement in the SF-36 PCS score compared with the MCS score was consistently observed throughout the study; this difference was greatest at the last visit.

The percentage of subjects achieving SF-36 stabilization or improvement was variable over time and

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ranged from 27.6% to 42.4% (at time points for which there was at least 25 evaluable subjects).

EQ-5D

Mean EQ-5D health questionnaire scores decreased slightly from Baseline during the treatment period in SL0008. No changes from Baseline were observed in the median EQ-5D health questionnaire scores throughout the study.

In general, results of the shift analysis demonstrated that the majority of subjects maintained or had improved in health status during SL0008. With the exception of self-care, for which the majority of subjects reported no problems, the majority of subjects reported moderate problems in each of these domains both at Screening and after repeated epratuzumab treatment. The percentage of subjects reporting moderate problems was similar to Screening for these 4 domains and maintained their health status throughout the treatment period.

Mean utility scores were increased (range: 0.60 to 0.71 points) through Visit 49 (Year 3, Week 48) compared with Baseline (0.51 points).

Mean health state scores were increased (range: 56.09 to 67.25 points) through Visit 49 (Year 3, Week 48) compared with Baseline (49.53 points), indicating better health of the subjects. The mean change from Baseline for these health state scores ranged from 6.72 to 19.67 points (at time points for which there was at least 25 evaluable subjects), with values increasing with repeated epratuzumab treatment. At the last visit, the mean change from Baseline was 10.54 points.

Treatment failure

Fifty-eight of 203 subjects met the definition of treatment failure during SL0008. The most common prohibited medications used by subjects defined as treatment failures were corticosteroids or new/increase in immunosuppressants (19.2%); among these were methylprednisolone and prednisone (5.9% of subjects, each) and methylprednisolone sodium succinate (3.0% of subjects). Other prohibited medications used by subjects defined as treatment failures were used by 9.4% of subjects, and the most common of these medications were ascorbic acid with tocopherol, retinol, and zinc, and multivitamins (2.0% of subjects, each).

Corticosteroid use

The mean corticosteroid dose decreased from Baseline over time with repeated treatment with mean decreases ranging from 1.79 to 4.68mg/day (at time points for which there were at least 25 evaluable subjects). The median corticosteroid dose was 10.00mg/day at Baseline and Visit 1 of SL0008. After 6 months of treatment, the median corticosteroid dose decreased to 7.50mg/day, and this dose was maintained or further reduced for the remainder of the study; however, the median change from Baseline was 0mg/day at most visits.

At Baseline, 34.5% of subjects were taking 7.5mg/day or less, 49.3% of subjects were taking >7.5 to 20mg/day, and 14.3% were taking >20mg/day. During SL0008, the percentage of subjects receiving corticosteroids in the higher dose categories of >7.5 to 20mg/day and >20mg/day declined, while the percentage of subjects who had reduced their steroid dose down to none or >0 to 7.5mg/day increased. In

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addition, the percentage of subjects in the lowest corticosteroid dose category (>0 to 7.5mg/day) increased over time.

At Visit 1 of SL0008, 191 subjects (94.1%) were using corticosteroids; only 12 subjects were not using corticosteroids at Visit 1. Throughout the study, the percentage of subjects who discontinued usage increased, and the percentage of subjects reducing their corticosteroid dose ranged from 12.2% to 42.6% at time points for which there were at least 25 evaluable subjects. A small number of subjects increased their corticosteroid dose (range: 0% to 6.7%), but this increased dose was not allowed to increase above that of Baseline.

Time to severe flare

During SL0008, 55.1% of subjects experienced a new severe lupus flare (defined as a new BILAG level A disease in 1 body system or BILAG level B disease in more than 1 body system). Flares were reported most often in the musculoskeletal (38.8%), renal (36.7%), and mucocutaneous (34.7%) body systems. New severe flares were reported in the cardiorespiratory body system in 3 subjects (6.1%). The median time to severe lupus flare was 1.63 years.

Time to moderate or severe flare

During SL0008, 78.3% of subjects who were without a moderate or severe flare experienced a new moderate (at least 1 new BILAG Grade B relative to Visit 1) or severe (at least 1 new BILAG Grade A or at least 2 new BILAG Grade Bs relative to Visit 1) lupus flare. Of the subjects with a new moderate or severe flare, these flares were reported most often in the mucocutaneous (38.9%), renal (25.0%), and musculoskeletal (19.4%) body systems. New moderate or severe flares were reported in the cardiorespiratory body system in 2 subjects (5.6%). The median time to moderate or severe lupus flare was 0.27 years.

Time to sustained response

The median time to sustained BILAG response was 1.38 years, and the median time to first sustained response using a combined index was 1.84 years. This analysis was restricted to subjects who still had at least an A or 2 Bs at Visit 1 of SL0008, ie, those who had not responded in SL0007.

Time to withdrawal due to lack of efficacy

A total of 28 subjects (13.8%) withdrew due to lack of efficacy during the study. The median time to withdrawal due to lack of efficacy was inestimable. The Kaplan-Meier estimate of the cumulative proportion of subjects experiencing withdrawal due to lack of efficacy at the end of each year was as follows: 9.1% by the end of Year 1; 14.2% by the end of Year 2; 19.1% by the end of Year 3; and 19.1% by the end of Year 4 (end of study).

SLICC/ACR

A mean decrease from Baseline was observed at Visit 1/Screening of SL0008 that decreased further with repeated treatment to Visit 29 and was generally maintained for the duration of the study. However, as the SLICC/ACR total damage score is a measure of permanent damage, which cannot decrease, this decrease was unexpected and likely does not reflect the clinical situation.

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At all time points, at least 50% of the subjects had a SLICC/ACR total damage score of 0 (no permanent damage) or 1 (a single item present as having permanent damage). No change from Baseline was observed in the median SLICC/ACR total damage score during this study.

Additional efficacy variables: In general, the data for BILAG grades by body system show a shift from moderate to severe disease (grades of A/B) to mild disease (Grade C) or disease not currently present (Grade D). For the constitutional, neuropsychiatric, cardiorespiratory, gastrointestinal, and ophthalmic body systems, the majority of subjects had mild disease at Baseline and did not worsen during the study, and those with severe disease showed improvement over time. For the mucocutaneous and musculoskeletal body systems, the majority of subjects had severe disease at Baseline with a shift toward improvement over time. For the neuropsychiatric and cardiorespiratory body systems, the majority of subjects had mild disease at Baseline, and those with severe disease showed improvement over time.

For the renal body system, a grade of A at Baseline was an exclusionary criterion. For this body system during SL0008, the percentage of subjects with BILAG grades of A, B, or C remained relatively similar, and the percentage with Grade D increased. There was a small group of 4 subjects with worsening of BILAG renal scores at the last visit of the study compared with Baseline (grades of D/E at Baseline and Grade A at the last visit). None of these 4 subjects completed the study, and withdrawal occurred at different times of follow up. According to the narratives, no particular pattern of renal function worsening was observed in these subjects. All 4 subjects had pre existing renal conditions. Overall, no signal of worsening renal function was detected that was associated with epratuzumab for these subjects. The shift from a lack of disease activity at Baseline to severe renal disease at the last visit in these 4 subjects may have been due to the natural progression of lupus. For the hematology body system, a similar pattern in the shifts of BILAG grades over time was observed, which would be expected for these 2 related body systems. Results of the shift analysis for all body systems demonstrated that the majority of subjects did not experience worsening of BILAG-defined disease activity during SL0008.

Pharmacokinetics/pharmacodynamics results: Mean epratuzumab plasma concentrations were similar within the treatment cycles during the study with repeated epratuzumab administrations. In addition, the range of concentrations observed in SL0008 was similar to that observed during SL0007 for the same dosing regimen.

Immunologic results: In general, the percentage of subjects who had a positive result for autoantibodies was similar throughout SL0008. For anti-dsDNA, anti-Sm, and anti-Sm/anti-RNP, a small increase in the percentage of subjects who were negative at Baseline and positive during SL0008 and a small decrease in those who were positive at Baseline and positive during SL0008 were observed with repeated epratuzumab treatment. This increase and decrease were of similar magnitude for these antibodies and resulted in no change in the percentage of positive subjects in the All Subjects group.

Decreases were observed in the BILAG total score from Visit 1 at Week 48 for subjects who were positive and those who were negative for ANA, anti-dsDNA, anti-Sm, and anti Sm/anti RNP.

At Baseline, 49.2% of subjects had a positive LAC result, and this percentage decreased with repeated

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epratuzumab treatment. At Baseline, 41.8% of subjects had a positive anticardiolipin result, and this percentage remained similar for visits during the treatment period at which ≥50% of subjects were tested. Mean changes from Baseline in C3, CRP, and RF were small with repeated epratuzumab treatment.

Similar decreases were observed in the BILAG total score from Visit 1 at Week 48 for subjects who were positive and those who were negative for LAC and anticardiolipin. For CRP, similar decreases were observed for those subjects in the <10mg/L group and 10mg/L to 30mg/L groups; however, the decrease was larger for the >30mg/L group. For C3 and RF, similar decreases in BILAG total score were observed for the higher (≥median) and lower (<median) groups.

Immunoglobulin A and IgG levels did not change substantially throughout the study for visits at which ≥50% of subjects were tested; however, IgM levels decreased slightly.

Similar decreases were observed in the BILAG total score from Visit 1 at Week 48 for subjects who were determined to have lower (<median) and higher (≥median) values for IgA, IgG, and IgM. The percentage of subjects showing BILAG improvement was similar for subjects who were determined to have lower (<median) and higher (≥median) values for IgG and IgM; however, the percentage of subjects showing BILAG improvement was higher in subjects who had lower IgA levels compared to those with higher IgA levels.

Absolute median B cell counts fluctuated over time with a general decreasing trend with repeated epratuzumab treatment. Median percent of Baseline B cell counts decreased with repeated epratuzumab treatment. The median percent change from Baseline in B cell counts was -15.3% at Screening. The median percent change was -36.1% at the last visit.

Absolute median T cell counts fluctuated over time but with no consistent trend emerging. Median percent of Baseline T cell counts fluctuated over time with a general increasing trend with repeated epratuzumab treatment. The median percent change from Baseline in T cell counts was 3.2% at Screening and 5.4% at the last visit.

Similar decreases were observed in the BILAG total score from Visit 1 at Week 48 for subjects who were determined to have lower (<median) and higher (≥median) values for B cells and T cells. The percentage of subjects showing BILAG improvement was similar for subjects who were determined to have lower (< median) and higher (≥ median) values for B cells and T cells, and similar mean B cell and T cell levels were observed among subjects with and without BILAG improvement at Week 48.

Occurrence of immunogenicity in this subject population was typical for that observed after administration of a biological drug and was slightly increased with respect to that observed during SL0007. A total of 19 subjects (9.4%) became HAHA positive during the study; however, the development of the HAHA immunological response was slow, with a gradual increase in the percentage of subjects testing positive for HAHA during the first year of repeated epratuzumab treatment.

Mean plasma concentrations of epratuzumab were slightly lower in subjects that were HAHA positive compared with HAHA negative subjects.

For subjects who became HAHA positive during the study, the percentage of subjects who showed

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BILAG improvement was increased throughout the study compared to Visit 1/Screening. In addition, HAHA status did not have an effect on BILAG improvement, as the percentage of subjects who were HAHA positive and showed BILAG improvement was constant throughout the study. This finding is in agreement with the small effect of HAHA status on epratuzumab concentrations. At the last visit, 57.9% of subjects showed BILAG improvement compared with 36.8% at Visit 1/Screening.

Safety results:

- The Safety Population included 203 subjects who were administered study medication. The mean duration of exposure was 686.0 days, with a range of 75 to 1185 days. The mean number of individual infusions was 16.0, with a range of 1 to 28 infusions.
- A total of 192 subjects (94.6%) reported 1946 treatment-emergent adverse events (TEAEs.) A total of 51 subjects (25.1%) reported a severe TEAE, and 87 subjects (42.9%) reported a drug-related TEAE. In addition, 29 subjects (14.3%) discontinued study drug due to TEAEs. Serious AEs were reported by 57 subjects (28.1%), and 1 subject died during this study.
- Treatment-emergent AEs were most commonly reported in the system organ classes (SOCs) of Infections and infestations (68.0%) and Nervous system disorders (38.9%). The most commonly reported TEAEs (by preferred term [PT]) were urinary tract infection (24.6%), upper respiratory tract infection (23.2%), headache (19.7%), sinusitis (10.8%), and nausea and asthenia (9.9% each).
- The majority of TEAEs were reported during Year 1 of SL0008 (1041/1946 events, 53.5%), with 674/1946 events (34.6%) in Year 2 and 227/1946 events (11.7%) in Year 3. The incidence rate was greater in Year 1 than in Years 2 or 3 (568.7/100 vs 490.6/100 or 378.0/100 patient-years [pt-yrs]), suggesting no increased TEAE risk with repeated epratuzumab exposure.
- A total of 87 subjects (42.9%) reported at least 1 treatment-related TEAE. Treatment-related TEAEs were most common in the SOCs of Infections and infestations (22.7%) and Nervous system disorders (9.9%). The most commonly reported treatment-related TEAEs were upper respiratory tract infection (8.4%), urinary tract infection (7.9%), and headache (5.4%).
- The majority of TEAEs were mild or moderate in intensity. Severe TEAEs were reported by 25.1% of subjects. Severe TEAEs were most commonly reported in the SOCs of Musculoskeletal and connective tissue disorders (6.9%); Infections and infestations (4.9%); Nervous system disorders and Gastrointestinal disorders (3.4% each). The most commonly reported severe TEAEs (by PT) were SLE (3.0%), headache (2.0%), lupus nephritis (2.0%), and osteonecrosis (1.5%).
- A total of 57 subjects (28.1%) reported 98 treatment-emergent SAEs. These SAEs were most commonly reported in the SOCs of Infections and infestations (6.9%) and Musculoskeletal and connective tissue disorders (5.4%). The most commonly reported treatment-emergent SAEs (by PT) were SLE (3.4%), lupus nephritis (2.5%), and cholelithiasis (1.5%).

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- The majority of treatment-emergent SAEs reported during Year 1 of SL0008 (56/98 events, 57.1%), with 30 events in Year 2 and 12 events in Year 3. The exposure-adjusted incidence rate was greater in Year 1 than in Years 2 or 3 (30.6/100 vs 21.8/100 and 20.0/100 pt-yrs), suggesting a decreased SAE risk with repeated epratuzumab treatment.
- One death occurred during this study. The subject died as a result of cardiac failure chronic; the event was considered to be unlikely related to study drug.
- Seven pregnancies were reported during the study. Two of these pregnancies resulted in induced abortions, 1 pregnancy resulted in a spontaneous abortion (miscarriage), 1 pregnancy resulted in a normal birth, 2 pregnancies resulted in premature births, and 1 pregnancy resulted in a vacuum-assisted birth after intrauterine growth restriction and decreased amniotic fluid. In addition, a male subject reported a partner pregnancy while he was in the study, and the outcome of this pregnancy was the delivery of a healthy baby.
- A total of 29 subjects (14.3%) reported 35 TEAEs leading to discontinuation of study drug. These TEAEs were most commonly reported in the SOC categories of Renal and urinary disorders (3.0%), Pregnancy, puerperium, and perinatal conditions (2.5%), and Musculoskeletal and connective tissue disorders (2.5%). The most commonly reported TEAEs leading to discontinuation of study drug (by PT) were lupus nephritis (3.0%), SLE (2.5%), and pregnancy (1.5%).
- A total of 29 subjects (14.3%) reported 74 treatment-emergent infusion reactions. Treatment-emergent infusion reactions were most commonly reported in the SOCs of General disorders and administration site conditions (6.4%) and Nervous system disorders (5.4%). The incidences of treatment-emergent infusion reaction AEs were low, with all events reported at incidences of ≤2.5%. The most commonly reported infusion reactions were nausea (2.5%), and headache, dizziness, and flushing (2.0% each).
- The majority of infusion reaction TEAEs were reported during Year 1 of SL0008 (62 events, 83.8%), with 8 events in Year 2 and 4 events in Year 3. The exposure-adjusted incidence of TEAEs was notably greater during Year 1 than in Years 2 or 3 (33.9/100 pt-yrs vs 5.8/100 pt-yrs and 6.7/100 pt-yrs), suggesting no increased TEAE risk of infusion reactions with repeated epratuzumab treatment.
- The most commonly reported TEAEs during the study were reported in the SOC of Infections and infestations (68.0%). The most common infection TEAEs were urinary tract infection (24.6%), upper respiratory tract infection (23.2%), and sinusitis (10.8%). The exposure-adjusted incidence rate for the SOC of Infections and infestations decreased over time, suggesting no increased TEAE risk of infections with repeated epratuzumab treatment. Severe infections were reported in 4.9% of subjects, and urosepsis was the only severe infection reported in more than 1 subject (2 subjects [1.0%]).
- Serious infections were reported by 14 subjects (6.9%). The only SAEs of Infections and infestations

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reported in more than 1 subject were gastroenteritis, sepsis, and urosepsis (2 subjects, each [1.0%]). The exposure-adjusted incidence rate of serious infections decreased from Year 1 to Year 2 and Year 1 to Year 3, indicating no increase in risk of serious infection TEAEs. Serious infections were reported most often during Year 1.

- Treatment-emergent AEs of depression were reported by 16 subjects (7.9%; 18 events); 2 events were serious. One subject reported attempted suicide.
- A total of 16 subjects (7.9%) reported TEAEs in the SOC of Neoplasms benign, malignant, and unspecified during the study. The reported malignancies in this SOC were thyroid neoplasm (2 subjects, 1.0%) and basal cell carcinoma, breast cancer, and lip neoplasm malignant stage unspecified (1 subject, 0.5% each). The exposure-adjusted incidence rate for this SOC decreased over time, and the incidences of the reported malignancies were low, indicating no increased risk of malignancies with repeated epratuzumab treatment.
- Serious AEs in the SOC of Neoplasms benign, malignant, and unspecified were reported by 3 subjects (1.5%). Of these SAEs, the reported malignancies were basal cell carcinoma, breast cancer, and lip neoplasm malignant stage unspecified (1 subject each [0.5%]). All of these SAEs were considered not related to study drug. The exposure-adjusted incidence rates for these SAEs do not indicate an increased risk of malignancies over time as basal cell carcinoma and lip neoplasm malignant stage unspecified only occurred during Year 1 and the only event of breast cancer occurred during Year 3.
- There were no consistent or clinically meaningful changes in hematology, serum chemistry, or urinalysis parameters or in the mean changes from Baseline throughout the study. There was no indication of an effect of epratuzumab on these laboratory parameters. Few subjects shifted to severe and life-threatening values (Grade 3 and Grade 4, respectively) in hematology or serum chemistry laboratory parameters. None of the AEs associated with these shifts to Grade 4 were considered to be related to study drug by the investigator.
- The most commonly reported TEAEs related to hematology parameters (by PT) were iron deficiency anaemia (12 subjects [5.9%]), leukopenia (10 subjects [4.9%]), anaemia (9 subjects [4.4%]), lymphopenia (6 subjects [3.0%]), and WBC count decreased (2 subjects [1.0%]). No other hematology-related TEAEs were reported for more than 1 subject. Adverse events of iron deficiency anaemia and anaemia could have been related to the study disease and were expected in this study population. Further, since epratuzumab can cause a reduction of peripheral blood B cell numbers, it was not unexpected to see some decreases in WBCs in subjects.
- The most commonly reported TEAEs related to serum chemistry parameters (by PT) were hypokalaemia (10 subjects [4.9%]), hypercholesterolemia (8 subjects [3.9%]), and aspartate aminotransferase increased (7 subjects [3.4%]).

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- The most commonly reported TEAEs related to urinalysis parameters (by PT) were pyuria (5 subjects [2.5%]), proteinuria (4 subjects [2.0%]), haematuria (4 subjects [2.0%]), glycosuria (2 subjects [1.0%]), and creatinine urine increased (2 subjects [1.0%]). No other urinalysis-related TEAEs were reported for more than 1 subject.
- No clinically relevant changes were observed for vital sign parameters (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) or body weight during the study. In addition, all pre- and postinfusional vital sign measurements remained within acceptable levels.
- The most commonly reported TEAEs related to vital signs (by PT) were hypertension (18 subjects [8.9%]), dyspnoea (15 subjects [7.4%]), and cough (13 subjects [6.4%]). All other TEAEs related to vital signs were reported in ≤2.0% of subjects.
- In general, most of the abnormal physical examination findings were consistent with the effect of SLE across many body systems.

Conclusions:

- The safety profile of epratuzumab 1200mg biweekly for a total of 2 doses in 12-week retreatment cycles, in moderate to severe systemic lupus subjects was similar to that observed in previous studies. No new safety signals were identified with long-term use.
- Subjects continued to show efficacy and improvements in HRQoL with repeated, long-term epratuzumab treatment.
- Results from specific safety analyses designed to assess the effect of epratuzumab on the subject's immune system indicated the generation of anti-epratuzumab antibodies; however, the development of this immunological response was slow and did not affect the efficacy of epratuzumab in terms of BILAG improvement.
- Long-term treatment with epratuzumab resulted in an approximate 50% to 60% reduction in peripheral B cells, with no noticeable effects on T cell numbers. Median levels of IgA, IgG, and IgM stayed within normal levels at all time periods; however, minor reductions in IgM were noted over time.
- The results of this study support the continued development of epratuzumab in patients with moderate to severe SLE.

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