SL0007, 2007-002566-35

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.

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Smyrna, GA 30080

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Official study title:

A phase IIb randomized, double-blind, placebo-controlled, dose and dose regimen-ranging study of the safety and efficacy of epratuzumab in serologically-positive systemic lupus erythematosus patients with active disease

CLINICAL STUDY REPORT SYNOPSIS: SL0007

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Name of active ingredient: Epratuzumab	**Page:** Not applicable	

Title of study: A phase IIb randomized, double-blind, placebo-controlled, dose and dose regimen-ranging study of the safety and efficacy of epratuzumab in serologically-positive systemic lupus erythematosus patients with active disease

Investigator(s): This was a multicenter study; 59 investigative sites were initiated.

Study site(s): This was a multicenter study; 59 sites were initiated (52 sites screened at least 1 subject and 47 sites randomized at least 1 subject).

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

Studied period: The total duration of the study for each subject was a maximum of 24 weeks. **First subject enrolled:** 29 Jan 2008 **Last subject completed:** 17 Aug 2009	**Phase of development:** Phase 2b

Objective(s): The primary objective of the study was to assess the dose response (4 dose groups) and the dose frequency (every other week [QOW] vs once a week [QW] dosed for a total of 4 weeks for a total of either 2 active or 4 active doses) of epratuzumab, versus placebo (PBO) during one 12-week treatment cycle in moderate to severe systemic lupus subjects with active disease.

Secondary objectives of the study were:

- To assess the safety of epratuzumab
- To optimize knowledge about efficacy assessments to be carried to Phase 3 confirmatory studies
- To assess the kinetics and attributes of B and T cells in circulation
- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of epratuzumab over a dose range, including exposure-response modeling and immunogenicity assessments
- To explore candidate biomarkers and gene expression relative to risk, prognosis, and response to epratuzumab treatment
- To assess the health-related quality of life (HRQOL) benefits of epratuzumab treatment
- To explore the utility benefits of epratuzumab treatment

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Exploratory objectives of the study were:

- To assess the cumulative steroid doses at Week 12 (Visit 10)
- To assess the proportion of subjects with a ≥20% reduction in steroid dose at Week 12 compared to Week 0 (Visit 2)
- To assess the time to first sustained response (as measured by primary endpoint analysis)
- To assess the time to enhanced British Isles Lupus Assessment Group (BILAG) response (As and Bs being reduced to ≤Cs) with sustained response at 2 consecutive visits, and with or without sustained response at all subsequent visits

Methodology: This was a 24-week, randomized, double-blind, PBO-controlled, dose and dose regimen-ranging study. Serologically positive systemic lupus erythematosus (SLE) subjects with moderate or severe disease who enrolled in the study entered a 14-day Screening Period. Eligible subjects were randomized in an equal ratio to 1 of 6 treatment groups; 5 epratuzumab groups (100mg, 400mg, 1200mg, or 1800mg QOW or 600mg QW) and 1 PBO group. Randomization was stratified according to disease severity (BILAG A grade presence/absence) and use of concomitant immunosuppressant medication (yes/no).

During the 12-week, double-blind Treatment Period, subjects received a total of 4 intravenous (iv) infusions at Weeks 0, 1, 2, and 3 of epratuzumab or PBO, in addition to any other standard SLE medications (corticosteroids, and possibly immunosuppressants and/or antimalarials) that the subject had continued from Baseline. At the end of the Treatment Period, subjects who had completed Week 12 and those who had discontinued the study at Week 8 or later due to treatment failure had the option of continued treatment in an open-label, long-term study (SL0008). Subjects who completed the 12-week Treatment Period but elected not to enter SL0008 were followed up for an additional 12 weeks with the Safety Follow-Up Visit occurring at Week 24. Subjects who discontinued the study prematurely and did not enter SL0008 had to return to the clinic 12 weeks after their final dose of study medication to complete the Safety Follow-Up Visit. The end of the study was defined as the final subject's last visit.

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Number of subjects (planned and analyzed): 200 to 210 subjects were planned to be enrolled (30 to 35 per treatment group); ultimately 310 subjects were enrolled and 227 subjects were randomized to receive either PBO (38 subjects) or epratuzumab 100mg (39 subjects), 400mg (38 subjects), 1200mg (37 subjects), or 1800mg (38 subjects) QOW or 600mg (37 subjects) QW.

Diagnosis and main criteria for inclusion: Subjects enrolled were male or female; ≥18 years of age; with a diagnosis of SLE as defined by the American College of Rheumatology (ACR)(≥4 criteria met); active moderate or severe SLE disease activity as demonstrated by BILAG A level disease activity in at least 1 body/organ system (except renal or neuropsychiatry), or BILAG B level disease activity in at least 2 body/organ systems (at least 1 BILAG A OR 2 BILAG Bs must have been in the mucocutaneous, musculoskeletal, or cardiovascular/respiratory body/organ systems), and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI total score ≥6 at Visit 1 [Screening]); and a positive antinuclear antibody (ANA) result at Visit 1. Other main inclusion criteria included the following:

- Were on a stable dose regimen of oral corticosteroids (range of 5 to 60mg/day prednisone [or equivalent]) for at least 5 days prior to Visit 2 (first study drug infusion).
- If on immunosuppressants, were on a stable dose regimen for 28 days (-1 day) prior to Visit 2.
- If on antimalarials, must have received antimalarials for at least 12 weeks, and were on a stable dose regimen for at least 28 days (-1 day) prior to Visit 2.

Test product, dose(s) and mode of administration, batch number(s): Epratuzumab at a concentration of 10mg/mL prepared in 17.5mL glass vials for slow iv infusion using only phosphate-buffered saline (PBS) as a vehicle/buffer for the infusion procedure.

Batch numbers: [redacted]

Duration of treatment: The duration of treatment was one 12-week treatment cycle.

Reference therapy, dose(s) and mode of administration, batch number(s): Placebo was sterile 0.04M PBS with 0.075% polysorbate 80, pH 7.4. Batch numbers: [redacted]

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Name of active ingredient: Epratuzumab	**Page:** Not applicable	

Criteria for evaluation:

Efficacy: The primary efficacy variable was the responder rate (yes/no) at Week 12 according to a combined response index. This was a response variable evaluated at Week 12 incorporating the following criteria for achievement of responder status (ie, all criteria must have been met to achieve responder status):

- BILAG improvement, defined as BILAG As at study entry improved to B/C/D, BILAG Bs at study entry improved to C/D, and no BILAG worsening in other BILAG organ systems, such that there are no new BILAG As or 2 new BILAG Bs
- No worsening in SLEDAI total score compared to study entry
- No worsening in physician's global visual analog scale (VAS) assessment of disease activity ('no worsening' defined as less than 10% worsening) compared to study entry
- Subjects who were treatment failures could not be responders

Treatment failure was defined as an increase in (or addition of a new) immunosuppressant agent over Baseline treatment levels or any increase in (or addition of a new) antimalarial over Baseline treatment level (Visit 2), regardless of indication. Any increase in corticosteroid (regardless of route, except for intraocular, nasal, ear, and topical) over Baseline treatment level (Visit 2) for an indication of SLE or any iv, intra-articular (ia), or intramuscular (im) injections of corticosteroids for the treatment of SLE was considered treatment failure.

The secondary efficacy variables were:

1. Combined response index analysis described for the primary variable above, but measured at Week 4 and Week 8.
2. Combined response index analysis including an additional criteria of stabilization or improvement of 36-Item Short Form Health Survey (SF-36) response, measured at Week 4, Week 8, and Week 12.
3. Number and percent of subjects with BILAG improvement (as defined in the first component of the primary efficacy variable) at Week 4, Week 8, Week 12, and Week 24.
4. Change from Baseline in Total BILAG Score; BILAG grades were converted from A/B/C/D/E to numeric values of 9/3/1/0/0, respectively.
5. Change from Baseline in SLEDAI total score measured at Week 2, Week 4, Week 8, and Week 12.
6. Change from Baseline in physician's and patient's global assessment of disease activity

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

(PGA and PtGA, respectively) score (using 100mm VAS) at each time point measured.

7. Percentage of subjects who achieved SF-36 stabilization or improvement (defined as a reduction in the physical component summary [PCS] of no more than 0.8, and a reduction in each of the 8 domain scores of no more than 2.5) at Week 4, Week 8, and Week 12.
8. Change from Baseline in SF-36 PCS, mental component summary (MCS), and individual domain results at Week 4, Week 8, and Week 12.
9. European Quality of Life-5 Dimensions (EQ-5D) at Week 12.
10. Time to first sustained response (as measured by the primary efficacy variable analysis) with response demonstrated at 2 consecutive visits.
11. Proportion of subjects who met the criteria for treatment failure.
12. Time to sustained response, as measured by BILAG improvement, demonstrated at 2 consecutive visits, and with or without sustained response at all subsequent visits.

Exploratory efficacy variables were:

- Cumulative steroid doses at Week 12
- Proportion of subjects with a ≥20% reduction in steroid dose at Week 12 compared to Week 0 (Visit 2)
- Time to first response (as measured by the primary efficacy variable analysis)
- Time to enhanced BILAG response (A and B grades being reduced to ≤C grades) with sustained response at 2 consecutive visits and with or without sustained response at all subsequent visits

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

Pharmacokinetics/pharmacodynamics: The PD variables were:

- Time course of changes in B and T cells in the peripheral circulation (eg, maturity activation status) as measured by flow cytometry.
- Immunoglobulin production (IgG, IgA, and IgM) in the peripheral circulation.
- Characterization of the nature and time course of gene expression relevant to the inflammatory and immune response process. This variable was addressed in the gene expression substudy, the results of which are not included in this clinical study report.
- Assessment of relationship of autoantibodies: ANA, antibodies to extractable nuclear antigen (anti-ENA), Smith antibody (anti-Sm), ribonucleoprotein antibody (anti-RNP), and double-stranded deoxyribonucleic acid antibody (anti-dsDNA), and other lupus-related laboratory parameters: complement C3 (C3), lupus anticoagulant, C-reactive protein (CRP), anticardiolipin, and rheumatoid factor (RF) to prognosis and treatment response.

Safety: The safety variables were:

- 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
- The immunogenicity variables were:
- Analysis of blood samples to detect the presence of human anti-human antibodies (HAHA) specifically against epratuzumab
- Assessment of whether the presence of HAHA had any influence on the PK of epratuzumab

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Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

Statistical methods: The Intention-to-Treat (ITT) Population consisted of all randomized subjects. The Per-Protocol (PP) Population included all subjects belonging to the ITT Population who had no major protocol violations affecting the primary efficacy variable. The Enrolled Population (EP) consisted of all subjects who had a signed informed consent form, and had case report form data from the Screening Visit (Visit 1). The Safety Population included all ITT subjects who received at least a partial dose of the study medication.

All efficacy analyses were performed on the ITT Population, with the PP Population as a secondary analysis set.

All p-values were 2-sided, unless otherwise noted. Statistical analysis of the primary variable was performed at α=0.05 level of significance. All p-values presented in conjunction with secondary analyses of the primary variable and for secondary efficacy variables were considered exploratory in nature.

Analysis of the primary efficacy variable (the responder rate at Week 12, based on a combined response index, which included SLEDAI, PGA, and BILAG assessments [ie, SPB]) consisted of a logistic regression model, modeling the responder rate as a function of treatment group, controlling for Baseline disease severity (BILAG A presence/absence) and the use of concomitant immunosuppressant medication at Baseline (yes/no). An estimate of the overall effect of epratuzumab was computed. Estimation of the differences between each of the 5 epratuzumab arms and PBO was derived in an exploratory manner: odds ratio (OR) estimate with 95% confidence interval (CI). Response rate based on the primary efficacy variable was repeated for subgroup analyses.

Various supportive and sensitivity analyses based on alternative statistical models, stratification factors, and alternative BILAG scoring were also performed.

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

Summary and conclusions:

Subject disposition: A total of 310 subjects were enrolled and 227 subjects were randomized into the study. Two subjects, both randomized to the epratuzumab 600mg QW group, discontinued the study prior to receiving study medication; therefore, 225 subjects were included in the Safety Population.

Of the 227 subjects in the ITT Population, 199 subjects (87.7%) completed the Treatment Period. Completion rates were generally similar across treatment groups, and were the lowest in the epratuzumab 600mg QW group (78.4%). The most common reason for discontinuation was lack of efficacy (4.8%), AE (2.6%), loss of efficacy (2.2%), protocol violation (1.3%), other reasons (0.9%), and withdrawal of consent (0.4%). Most subjects (89.4%) entered the open-label extension study (SL0008).

Efficacy results: Treatment with epratuzumab did not demonstrate a statistically significant difference from PBO in the SPB responder rate at Week 12 (primary efficacy variable); however, a treatment effect of epratuzumab in adult subjects with moderate to severe SLE was observed.

Epratuzumab demonstrated a clinically meaningful improvement in the 2400mg cumulative dose groups (600mg QW and 1200mg QOW) in comparison to PBO using the selected SPB index to measure response. Results of this study support the testing of the cumulative treatment cycle dose of 2400mg, administered as 4 doses of 600mg QW for 4 weeks or as 2 doses of 1200mg administered QOW in future studies.

The results of the secondary efficacy variables related to the BILAG or SLEDAI support the improvements observed in the primary efficacy variable in the epratuzumab 2400mg cumulative dose groups (600mg QW and 1200mg QOW); however, none of the other efficacy variables (PGA, PtGA, and cumulative corticosteroid dose) or assessments of HRQoL (SF-36 and EQ-5D) showed meaningful improvements over PBO. The inability to detect treatment differences was likely due to the short 12-week Treatment Period. Longer studies with repeated dosing may show a better separation of epratuzumab from PBO for such measurements.

Primary efficacy variable

The primary efficacy variable was the SPB responder rate at Week 12, based on a combined response index, which included SLEDAI, PGA, and BILAG assessments. At Week 12, all individual epratuzumab groups showed higher SPB responder rates than PBO (21.1%). The highest SPB responder rates were observed in the epratuzumab 2400mg cumulative dose groups (600mg QW and 1200mg QOW groups), with the epratuzumab

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Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

600mg QW group (45.9%) having a higher value than the epratuzumab 1200mg QOW group (40.5%). Responder rates and treatment differences for both the epratuzumab 600mg QW group and the 1200mg QOW group were considered clinically meaningful improvements over PBO.

The overall test of epratuzumab treatment effect was not statistically significant; however, subjects in the epratuzumab 600mg QW and 1200mg QOW groups were 3.17 times (95% CI: 1.14, 8.79) and 2.57 times (95% CI: 0.92, 7.12) more likely to be a SPB responder than subjects in the PBO group, respectively.

Secondary analysis of the primary efficacy variable

Various supportive and sensitivity analyses based on alternative statistical models, stratification factors, and alternative BILAG scoring revealed results similar to the primary analysis, indicating consistency and robustness of the results.

Secondary efficacy variables

SPB response at Weeks 4 and 8

- The overall test of epratuzumab treatment effect was not statistically significant; however, clinical meaningful improvements over PBO were observed as early as Week 4 in the epratuzumab 600mg QW group, and as early as Week 8 for the epratuzumab 1200mg QOW group.

SPB response plus SF-36

- The SPB responses at Weeks 4, 8, and 12 were considerably depressed across all treatment groups by the addition of the SF-36 compared with the SPB responder rate in the primary efficacy analysis.

Time to first sustained SPB response

- There were no significant differences between each epratuzumab group and PBO for time to first sustained SPB response. Even so, subjects in the epratuzumab 2400mg cumulative dose groups (600mg QW and 1200mg QOW) were 1.84 and 1.63 times as likely to have a sustained SPB response at any point in time than subjects in the PBO group, respectively. For subjects in the remaining epratuzumab groups (100mg, 400mg, and 1800mg QOW), a difference from PBO in time to sustained SPB response was less apparent.

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

Time to first sustained BILAG response

- There were no significant differences between each epratuzumab group and PBO for time to first sustained BILAG response. Subjects in the epratuzumab 2400mg cumulative dose groups (600mg QW and 1200mg QOW) were 1.95 and 1.47 times as likely to have a sustained BILAG response at any point in time than subjects in the PBO group. For subjects in the remaining epratuzumab groups (100mg, 400mg, and 1800mg QOW), a difference from PBO in time to sustained BILAG response was less apparent.

Treatment failure

- The percentage of subjects who met the criteria for treatment failure was similar across most treatment groups (range: 10.5% to 15.8%), except in the epratuzumab 600mg QW group (29.7%). The most common reasons for treatment failure were withdrawal from study, increased corticosteroid dose, and increased immunosuppressant dose.
- No subjects in the study were considered treatment failures for taking prohibited medication or increasing their dose of antimalarials.

BILAG improvement

- BILAG improvement was more pronounced in the epratuzumab 600mg QW group (62.1% and 51.4%) than in the epratuzumab 1200mg QOW group (44.1% and 40.5%) or PBO group (30.6% and 28.9%) at Week 12 and End of Treatment, respectively. The percentage of subjects with BILAG improvement in the other epratuzumab groups was similar to PBO across visits. BILAG improvement was seen as early as Week 4 for the epratuzumab 600mg QW group and as early as Week 8 for the epratuzumab 1200mg QOW group compared with PBO.

Enhanced BILAG response

- Approximately 20% of subjects in the epratuzumab 2400mg cumulative dose groups (600mg QW and 1200mg QOW groups) had enhanced BILAG improvement over the course of the study compared with 13.9% of PBO subjects. The other epratuzumab groups showed BILAG improvement similar to PBO. There were no meaningful differences in time to first sustained enhanced BILAG response.

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

BILAG grades over time

- In general, a lower percentage of subjects had BILAG A or B grades at the End of Treatment compared to Baseline across all treatment groups in the musculoskeletal, mucocutaneous, cardiorespiratory, neuropsychiatric, constitutional, ophthalmic, and renal body systems. In the renal body system, where BILAG A was not permitted for inclusion in the study, an increase in the percentage of subjects with BILAG A or B grades at the End of Treatment was seen in the epratuzumab 100mg and 1800mg QOW groups.
- Most subjects in each treatment group improved their disease activity to BILAG D or E at End of Treatment in the constitutional, neuropsychiatric, cardiorespiratory, ophthalmic, and renal body systems.
- In the musculoskeletal and mucocutaneous body systems, more subjects in the epratuzumab 600mg QW and 1200mg QOW groups improved their disease activity to BILAG D or E at End of Treatment compared with PBO.

BILAG grades among subjects with flares at Baseline

- Among subjects with flares at Baseline, improvements in disease activity over PBO were observed in the epratuzumab groups compared with PBO at End of Treatment in the musculoskeletal, mucocutaneous, cardiorespiratory, neuropsychiatric, constitutional, and renal body systems.
- A higher percentage of subjects receiving epratuzumab 600mg QW improved their disease activity to a BILAG D compared with PBO at End of Treatment. Efficacy was particularly prominent in cardiorespiratory and neuropsychiatric systems, in which symptom improvements are often difficult to achieve.
- A higher percentage of subjects receiving epratuzumab 1200mg QOW improved their disease activity to a BILAG C or D compared with PBO in the musculoskeletal, mucocutaneous, neuropsychiatric, and renal systems.

Shifts in BILAG grade from Baseline to worst post-Baseline BILAG

- Results of the shift analysis for all body systems, except the musculoskeletal and mucocutaneous body systems, did not reveal any trends in shifts that showed differences between the epratuzumab groups and PBO.

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

<u>BILAG total score using the numeric conversion</u>

- Using the numeric conversion 9/3/1/0/0 or 12/6/1/0/0, the epratuzumab 600mg QW group showed a statistically significant reduction (improvement) from Baseline in the BILAG total score over PBO at Weeks 8 and 12 and a meaningful reduction at End of Treatment. Reductions from Baseline in BILAG total score in the epratuzumab 600mg group were evident from Week 4. The epratuzumab 1200mg QOW group also showed reductions in BILAG total score over PBO, with clinically meaningful reductions at Week 8 for conversion 12/6/1/0/0. No other epratuzumab groups showed clinical improvements from Baseline in BILAG total score over PBO at Weeks 4, 8, 12, and End of Treatment.
- Using the numeric conversion 9/3/1/0/0 or 12/6/1/0/0, repeated measures analysis of the epratuzumab 600mg QW group showed a statistically significant reduction from Baseline in BILAG total score over time versus PBO. Reductions from Baseline in BILAG total score were also seen in the epratuzumab 1200mg QOW group over PBO. No other epratuzumab group showed any improvement from Baseline over PBO in BILAG total score.
- Using the time-weighted AUCMB, differences in BILAG total score between each epratuzumab groups and PBO using LS means were not statistically significant. However, this method confirmed a greater reduction in the BILAG total score in the epratuzumab 600mg QW and the epratuzumab 1200mg QOW group compared with PBO. Both these results were considered meaningful.

<u>BILAG B grade inflation</u>

- Few subjects shifted from a BILAG C post-Baseline to BILAG B with no worsening of symptoms (BILAG B inflation) in the neuropsychiatric, constitutional, cardiorespiratory, gastrointestinal, and ophthalmic body systems. However, it is noteworthy that it did happen at all, as this "inflation" represents subjects with a BILAG grade that worsened from one visit to the next without any corresponding worsening in their condition.

<u>SLEDAI</u>

- There were no statistically significant treatment differences from Baseline in the SLEDAI total score at Weeks 4, 8, 12 or End of Treatment over PBO; however, the mean time-weighted AUCMB was less than 0 for all groups, which indicated that the average effect over time was that SLEDAI total score was lower than Baseline values.

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

- Overall, between 76.3% and 97.3% of subjects had no worsening in SLEDAI total score (a component of the SPB response criteria) at the End of Treatment across all treatment groups. The percentage of subjects with no worsening in SLEDAI total score increased over time for the epratuzumab 2400mg cumulative dose groups.

PGA and PtGA

- There were no statistically significant reductions (improvements) from Baseline in mean PGA or PtGA.
- The percentages of subjects with no worsening in PGA (a component of the SPB response criteria) ranged from 81.3% to 97.0% at Week 12 and from 78.9% to 94.6% at End of Treatment for the epratuzumab groups compared with PBO (91.7% and 92.1%, respectively).

Health-related quality of life

- The HRQoL benefits of epratuzumab treatment were evaluated using the SF-36 and EQ-5D Questionnaires. At Baseline, all SF-36 domain scores across all treatment groups were very low compared with age- and gender-matched US norms in SLE patients. Mean SF-36 domain, PCS, and MCS scores across treatment groups generally increased over time from Baseline through End of Treatment. Most of the increases in the epratuzumab groups were either similar or less than the PBO response at each visit; therefore, no statistically significant increases from Baseline were observed.
- The epratuzumab 600mg QW group showed clinical meaningful improvements over PBO, defined as a treatment difference of ≥5.0, in the domain of vitality at Weeks 4, 8, 12, and End of Treatment.
- There were no statistically significant changes from Baseline in the EQ-5D Utility Scores at Week 12 or End of Treatment. The observed EQ-5D Health State (based on 100mm VAS) increased from Screening to Week 12 and End of Treatment, indicating a better health state, in most groups. Changes from Baseline were higher at Week 12 for the epratuzumab 600mg QW group compared with PBO.

Other efficacy variables

- The mean cumulative corticosteroid dose from randomization to Week 12 was generally similar across treatment groups. There were no statistically significant

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

differences in the cumulative corticosteroid doses between each epratuzumab group and PBO.

- The proportion of subjects who had a ≥20% reduction in corticosteroid dose at the End of Treatment was highest in the PBO group (23.7%). Due to the relatively low mean dose of corticosteroid at Baseline (13.7mg/day), it was not unexpected that relevant reductions in the corticosteroid dose were not observed.
- The difference in time to first response between the epratuzumab 600mg QW group and PBO was statistically significant (p=0.009). Subjects in the epratuzumab 600mg QW group were more than twice as likely to have a response at any point in time than subjects in the PBO group (hazard ratio: 2.46; 95% CI (1.23, 4.91).
- The differences in time to first sustained enhanced BILAG response between each epratuzumab group and PBO were not statistically significant.

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

Pharmacokinetics/pharmacodynamics results:

- Pharmacokinetics of epratuzumab appeared to be linear as concentrations increased proportionally with dose.
- B cell counts moderately decreased over time in all treatment groups, and were generally lower in the epratuzumab groups than PBO at most visits.
- No consistent trends in T cell counts were observed over time across treatment groups.
- There were no consistent differences in mean B cell counts for SPB responders and nonresponders based on SPB response, BILAG response, SLEDAI response, and PGA response.
- Median levels of IgA, IgG, and IgM stayed within normal levels at all time periods. There were no consistent differences across the treatment groups in mean IgA, IgG, and IgM levels for responders and nonresponders based on SPB response, BILAG response, SLEDAI response, and PGA response.
- There were no consistent trends observed across treatment groups in SPB response at Week 12 based on the presence or absence of ANA; or positive or negative anti-dsDNA, anti-Sm, or anti-RNP at Baseline.
- There were no consistent trends observed in mean C3, CRP mean RF levels or anticardiolipin status across treatment groups at Week 12 for SPB response, BILAG response, SLEDAI response, or PGA response.
- Flow cytometry analyses showed that the observed CD22+ B cell reduction was dose and time dependent. The remainder of the CD marker combinations analyzed suggested no significant changes in B cell subpopulations that could be readily attributed to epratuzumab dose or responder status of the subject.

Safety results: In this study, epratuzumab appears to have an acceptable safety profile across all doses investigated and over the entire 12-week Treatment Period (ie, 1 treatment cycle). No clinically relevant safety concerns were identified that would preclude further development of epratuzumab. Epratuzumab also appears to be generally well tolerated, since few subjects discontinued the study medication due to a TEAE. The occurrence of immunogenicity was low.

- The Safety Population included 187 subjects who received epratuzumab and 38 subjects who received PBO. During the 12-week Treatment Period, the mean

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

duration of exposure was similar across treatment groups. Most subjects (97.3%) received all 4 infusions of study drug.

- A similar percentage of epratuzumab-treated and PBO subjects experienced at least 1 TEAE (69.5% and 71.1%, respectively). The incidence of TEAEs was generally similar across treatment groups. The highest incidence and number of TEAEs were observed in the epratuzumab 1200mg QOW group (78.4% and 119 events, respectively).
- Across the epratuzumab and PBO treatment groups, TEAEs were most common in the infections and infestations SOC (30.5% and 26.3%, respectively). Within the infections and infestations SOC, URTI, UTI, and sinusitis were the 3 most commonly reported infections across all treatment groups.
- The most common TEAEs reported by epratuzumab-treated subjects (overall) compared with PBO were headache, nausea, URTI, and dizziness. A higher incidence of URTI (15.4%) and nausea (12.8%) and a lower incidence of headache (5.1%) were observed for subjects in the epratuzumab 1800mg QOW group, compared with those in the lower dose epratuzumab groups and PBO.
- A total of 28 subjects experienced an infusion reaction. The incidence of infusion reactions was similar between epratuzumab-treated (12.8%) and PBO-treated subjects (10.5%), and was generally similar across treatment groups. Most of the infusion reactions each occurred in only 1 subject. Only epratuzumab-treated subjects (17 subjects in total) reported nausea, dizziness, somnolence, and dyspnoea. Headache and flushing were each reported by a similar percentage of epratuzumab-treated and PBO subjects. One serious infusion reaction, anaphylactic reaction, was experienced by 1 subject in the epratuzumab 400mg QOW group.
- The percentage of subjects with AEs that were possibly indicative of infection was similar between the epratuzumab-treated (40.6%) and PBO subjects (39.5%), although these percentages were higher in the epratuzumab 1800mg QOW group (51.3%) and lower in the epratuzumab 400mg QOW group (24.3%) compared with PBO.
- The percentage of subjects who had treatment-related TEAEs was higher in epratuzumab-treated subjects compared with the PBO-treated subjects (33.7% and 21.1%, respectively). The most frequently reported treatment-related TEAEs across treatment groups were headache, nausea, UTI, diarrhea, dyspnoea, and dizziness. There did not appear to be a dose-related trend in the epratuzumab groups. Nausea, dizziness,

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Name of finished product: Not applicable	**Volume:** Not applicable	
Name of active ingredient: Epratuzumab	**Page:** Not applicable	

diarrhoea, and dyspnoea only occurred in epratuzumab-treated subjects.

- Most subjects had TEAEs that were considered mild or moderate in intensity. A total of 19 subjects experienced TEAEs of severe intensity.
- There were no deaths or pregnancies reported in this study.
- Sixteen subjects reported a total of 17 SAEs; incidences of SAEs were generally similar among treatment groups. No SAE was reported by more than 1 subject.
- Two subjects in the epratuzumab 1200mg QOW group experienced infections that were considered serious (abdominal abscess and UTI). One subject in the epratuzumab 400mg QOW group experienced an SAE of diarrhoea haemorrhagic that was considered possibly indicative of infection.
- Few subjects (7 subjects, 3.1%) permanently discontinued study medication and/or the study period due to a TEAE. There was no indication that treatment with epratuzumab lead to discontinuation more commonly than treatment with PBO.
- There were no consistent clinically meaningful differences or trends in Baseline hematology, serum chemistry, or urinalysis parameters or in the mean changes from Baseline to Week 12 and End of Treatment between treatment groups. There was no indication of an effect of epratuzumab on hematology, serum chemistry, or urinalysis laboratory parameters. There were no individual laboratory changes that appeared to be associated with epratuzumab treatment based on analysis of shifts from Baseline, individual clinically relevant laboratory events, or AEs related to laboratory parameters.
- The mean values for the vital sign parameters (diastolic and systolic blood pressure, pulse rate, temperature and respiratory rate) remained within acceptable ranges in all treatment groups. Changes from Baseline and changes from pre-infusion to post-infusion were minimal and similar across treatment groups at all visits through Week 12 and End of Treatment.
- In general, most of the abnormal physical examination findings were consistent with the effect of SLE across many body systems and related to surgical and medical procedures that had been performed.
- Occurrence of immunogenicity in this subject population was low; 4 of the 187 epratuzumab-treated subjects met the criteria for a positive HAHA result at Week 12. There was no observed effect or correlation of the HAHA occurrence on the PK/PD, and there appeared to be no relationship between the AEs observed and the

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presence of a positive HAHA.

Conclusions:

- Epratuzumab demonstrated a clinically meaningful improvement in the 2400mg cumulative dose groups (600mg QW and 1200mg QOW groups) in comparison to PBO using the selected SPB index to measure response. Results of this study support the testing of the cumulative treatment cycle dose of 2400mg, administered as 4 doses of 600mg QW for 4 weeks or as 2 doses of 1200mg administered QOW in future studies.
- Overall analyses of safety data (AEs, clinical laboratory evaluations, vital sign measurements, etc) demonstrate that epratuzumab appears to have an acceptable safety profile, and is well tolerated in the treatment of moderate to severe SLE in adult subjects in this study. No untoward signals and no apparent dose-related toxicity were observed, and the risk-benefit ratio is considered positive at this point, based on available knowledge, thus supporting the further development of epratuzumab in the treatment of SLE.
- Results from specific safety analyses designed to assess the effect of epratuzumab on the subject's immune system showed an apparent low risk for the generation of anti-epratuzumab antibodies and only mild reduction of B cells following treatment with epratuzumab.

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