2 SYNOPSIS

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Forigerimod for injection		
Name of Active Ingredient: Forigerimod (CEP-33457)	**Volume:**	
	Reference:	

Title of Study: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a 200-mcg Dose of CEP-33457 in Patients With Systemic Lupus Erythematosus

Investigators and Study Centers: The study was conducted at 54 centers in the United States (US) and Europe by 54 investigators. A complete list of investigators and their affiliations is included in the clinical study report.

Publication (reference): Results from this study had not been published at the time of approval of this report.

Study Period: 24 June 2010 to 31 January 2012 **Phase of Development:** 2b

Primary Objective: The primary objective of the study was to evaluate the efficacy of a 200-mcg dose of CEP-33457 compared with placebo in patients with active systemic lupus erythematosus (SLE) as assessed by the proportion of patients with a combined clinical response using the SLE responder index (SRI) at week 24. An SRI response was defined as a reduction from baseline in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of at least 4 points, no worsening in the Physician's Global Assessment (PhGA) scale (with worsening defined as an increase in PhGA of more than 0.30 points [inches] from baseline), no new British Isles Lupus Assessment Group A (BILAG A) body system score, and no more than 1 new BILAG B body system score from baseline.

Secondary Objectives: The secondary objectives of the study were to assess the following:

- the proportion of patients achieving an SRI response at each visit during the treatment period
- the proportion of patients achieving a reduction of at least 4 points in the SLEDAI-2K total score at each visit during the treatment period
- the effect of CEP-33457 on disease activity, as assessed by the BILAG-2004 disease activity index, at each visit during the treatment period
- the effect of CEP-33457 on the status of disease (PhGA and Patient's Global Assessment [PtGA] scales) at each visit during the treatment period
- the effect of CEP-33457 on health-related quality of life, as assessed by completion of the Medical Outcome Survey Short Form 36 (SF-36) at week 12 and the final assessment (week 24 or early termination)

The exploratory efficacy objectives of the study were to determine the following:

- the effect of CEP-33457 on arthritis, as assessed by the 28-joint count examination for pain and tenderness at each visit during the treatment period
- the effect of CEP-33457 on the cutaneous manifestations of disease, as assessed by the Cutaneous Lupus Erythematosus Disease Area and Severity Index at each visit during the treatment period
- the effect of CEP-33457 on the following biologic markers of disease activity at each visit during the treatment period:
  - anti–double-stranded deoxyribonucleic acid antibody (anti-dsDNA Ab)
  - complement components (C3 and C4)
- the effect of CEP-33457 on the following biologic markers of disease activity at weeks 4 and 12 and the final assessment (week 24 or early termination):
  - antinuclear antibodies (ANA)
  - anti–U1 ribonucleoprotein antibody
  - anti-Smith antibody

  - C-reactive protein
  - immunoglobulin G, immunoglobulin M, and immunoglobulin E
  - interleukin-6 and interleukin-10
  - B- and T-cell subsets as assessed by immunophenotyping
- the effect of CEP-33457 on the incidence of disease flares (ie, Safety of Estrogens in Lupus Erythematosus: National Assessment Flare Index and SLEDAI-2K score of greater than 15) at each visit during the treatment period
- the effect of CEP-33457 on the occurrence of SLE-induced organ damage (eg, Systemic Lupus International Collaborative Clinics/American College of Rheumatology [ACR] Damage Index and adverse event inquiry) at the final assessment (week 24 or early termination)
- the proportion of patients with changes in steroid dose over time throughout the study
- the effect of CEP-33457 on health-related quality of life (QoL), as assessed by completion of the Lupus QoL Questionnaire at week 12 and the final assessment (week 24 or early termination)

Number of Patients (Planned and Analyzed): For this study, 220 patients were planned to be enrolled; data from 182 patients were analyzed for efficacy and data from 183 patients were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Patients were included in the study if all of the following main criteria were met (not all inclusive): The patient was a man or woman between 18 and 70 years of age with established SLE, and met at least 4 SLE criteria as defined by the ACR Classification Revised Criteria. The patient had a positive test for ANA and/or a positive test for anti-dsDNA Ab at screening. The patient had a clinical SLEDAI-2K score of at least 6 points during screening, and the patient did not have an "A" score (very active disease) on the BILAG-2004 scale. If the patient was using oral corticosteroids, the cumulative dose must not have exceeded 80 mg/week of prednisone equivalent, and the weekly dose had to be stable over the 4 weeks preceding the first dose of study drug. There were also other requirements regarding the types and dosages for SLE treatments. Women must have been surgically sterile, 2 years postmenopausal, or using contraception.

Main Criteria for Exclusion: Patients were excluded from this study if 1 or more of the following main criteria were met (not all inclusive): The patient had been treated with intramuscular or intravenous (iv) pulse steroids (250 to 1000 mg iv total daily dose of methylprednisolone) within 4 weeks of the first dose of study drug; the patient received tacrolimus, cyclosporine A, or iv immunoglobulins (IVIG) within 3 months of the first dose of study drug; the patient received cyclophosphamide, or SLE treatments such as fusion proteins, therapeutic proteins, or monoclonal antibodies or antibody fragments, within 12 months of the first dose of study drug; the patient received B-cell depleting agents such as rituximab and the B-cell count had not yet normalized (CD20+ B-cell count was less than 200 and the absolute lymphocyte count was less than 1500/µL). Patients were also excluded if they had congestive heart failure, severe active lupus nephritis or cerebritis, an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, specified liver function test abnormalities, clinically significant abnormalities on the 12-lead electrocardiogram (ECG) not related to SLE, a history of alcohol or substance dependence or abuse, an ongoing active systemic infection requiring treatment, or a history of severe infection in the 3 months before the first dose of study drug. Pregnant and lactating women were also excluded.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: CEP-33457 is a white to off-white, amorphous powder supplied in single-dose glass vials (3 vials per carton) as lyophilized product for reconstitution. Each vial contained 200 mcg of CEP-33457, trehalose dihydrate, and acetic acid and was reconstituted with 1.1 mL of sterile water for subcutaneous (sc) injection. Patients assigned to CEP-33457 were given 200 mcg sc every 4 weeks for 20 weeks (per final protocol, Amendment 5), or up to 44 weeks for those enrolled under Amendment 4. CEP-33457 lot numbers used in this study were 09DD003A503, 10DD002A503, and 10DD007A503 (last number revised to 10-000963).

Placebo: Placebo vials matching the single-dose vials of CEP-33457 were supplied by Cephalon, Inc. Each placebo vial contained a white to off-white, amorphous powder as a lyophilized sterile formulation of trehalose dihydrate and acetic acid (3 vials per carton), and was reconstituted with 1.1 mL of sterile water for injection. Patients assigned to placebo were given placebo sc every 4 weeks for 20 weeks (per final protocol, Amendment 5), or up to 44 weeks for those enrolled under

Amendment 4. The placebo lot numbers were 09DD002A503, 10DD001A503, and 10DD006A503 (last number revised to 10-000921).

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: Patients were randomly assigned to 1 of 2 treatment groups using an interactive voice response system. The randomization was stratified by region (US or non-US, SLEDAI-2K screening total score [6 to 9 or ≥10], and racial-ethnic group classification [black/Hispanic or others]).

Duration of Treatment: The study consisted of a screening period, a 20-week treatment period, and a final assessment done 4 weeks after the last dose of study drug. The final assessment could be on week 24 or after early termination (per final protocol, Amendment 5), or up to week 48 for patients enrolled when the treatment period was extended to 44 weeks in protocol Amendment 4.

General Design and Methodology: This was a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a 200-mcg dose of CEP-33457 compared with placebo in patients with active SLE. At the screening visit, medical, psychiatric, and medication histories were obtained, and physical examinations were performed. Disease activity was assessed using the SLEDAI-2K and BILAG-2004 disease activity indices, disease marker testing (eg, anti-dsDNA Ab, ANA, complement), and the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index. At baseline, patients were randomly assigned (and stratified as indicated above) to receive either CEP-33457 or placebo. Study drug was given after the assessments. Patients returned to the study center every 4 weeks for assessments and to receive either CEP-33457 or placebo sc. Patients could continue on their usual treatment for SLE (ie, standard of care) as long as the inclusion and exclusion criteria for these treatments were met; the dosages for immunosuppressive medications could have changed, if needed, only as directed in the protocol.

Primary Efficacy Measure(s) and Endpoint(s): The primary efficacy variable was the proportion of SRI responders at week 24. Patients who withdrew before week 24 were classified as nonresponders.

Secondary Efficacy Measures and Endpoints: The secondary efficacy variables and endpoints assessed at the visits during the treatment period were as follows:

- the proportion of patients with an SRI response
- the proportion of patients with a reduction of at least 4 points in the SLEDAI-2K total score
- the proportion of patients with a clinical SLEDAI-2K response, in which the clinical response was defined as a reduction of at least 4 points in the SLEDAI-2K clinical score
- the proportion of patients with a BILAG-2004 response (no new A body system score and no more than 1 new BILAG B body system score from baseline). The BILAG-2004 includes 97 items to evaluate SLE disease activity in 9 organ systems; scores are graded from A (very active disease) to E (no current disease activity and the organ system has never been involved).
- the proportion of patients with a BILAG-2004 clinical response (improvement in at least 1 category from a B score to a C or D score, with no worsening in any other category)
- the proportion of patients showing no worsening on the PhGA and PtGA
- absolute and relative changes in the SF-36 at week 12 and the final assessment (week 24 or early termination)

Exploratory efficacy variables and endpoints are discussed in the clinical study report.

Safety Variables: Safety and tolerability were assessed by evaluating adverse events (including deaths, serious adverse events, and withdrawals due to adverse events), clinical laboratory test results (serum chemistry, hematology, and urinalysis), vital signs measurements (eg, blood pressure, pulse), 12-lead ECGs, physical examinations, and concomitant medication usage.

Pharmacokinetics: Blood samples were obtained between 5 and 15 minutes after study drug administration from approximately 20 patients at selected study centers in the US to measure plasma concentrations of CEP-33457; these samples could be taken at any visit during the treatment period.

Immunogenicity: Immunogenicity was assessed by detection of the presence or absence of specific anti-CEP-33457 antibodies (Abs) at week 12 and the final assessment.

Statistical Considerations: Patients in the safety analysis set took at least 1 dose of study drug. The full analysis set for efficacy included patients in the safety analysis set who had the baseline SLEDAI-2K total

score, BILAG-2004 body system scores, and the PhGA score. The completer analysis set included patients who completed the study at week 24 or later. This study needed to enroll approximately 220 patients to provide 100 evaluable patients per group, to have 80% or more power to detect a 20% or more difference in the proportion of SRI responders between the CEP-33457 and placebo groups. This projection using the Pearson Chi-square test (2-sided, alpha=0.05) was based on an anticipated placebo effect at week 24 up to 60%. For the SRI, a logistic regression model with treatment and stratification factors as main factors was used and was linked to the model factors through the logit function. Likelihood ratio based Chi-square statistics were used for testing the treatment difference at the significance level 0.05. The goodness of fit for the final main effect model was evaluated by the ratio of deviance over degrees of freedom and the scaled Chi-square statistics. The parameters were estimated using the maximum likelihood method. The odds ratio (active/placebo) and associated 95% confidence interval were determined from the logistic regression model. An interim analysis based on a secondary endpoint was performed when at least 80 patients had completed week 12 or had been withdrawn from the study; this was for designing future studies, not for determining whether the study would be continued, so no stopping rules were defined. All efficacy variables were summarized by treatment group and time point. For the responder analyses and categorical variables, the same logistic regression model was used as for the primary analysis. For the continuous variables, an analysis of variance model was used with treatment and stratification factors as fixed factors. If not stated otherwise, all statistical inferences for secondary efficacy analyses were based on 2-sided tests at a nominal level of 0.05. The SLEDAI-2K, BILAG-2004, PhGA, PtGA, and SF-36 results were summarized using descriptive statistics. Descriptive statistics for continuous variables included number (n), mean, standard deviation (SD), standard error (SE) of the mean, median, minimum, and maximum. Descriptive statistics for categorical variables included patient counts and percentages.

Summary of Results

Patient Disposition and Demography: This study was stopped before 220 patients were enrolled so enrollment was slightly smaller than planned; there were no safety issues. Patients were enrolled at 28 centers in the US and 26 in Europe. Of the 319 patients screened, 183 were randomly assigned to treatment (91 to CEP-33457; 92 to placebo), received at least 1 dose of study drug, and were evaluable for safety. The full analysis set evaluable for efficacy included 182 (>99%) patients, and 144 (79%) completed the study with at least 24 weeks of double-blind treatment. The average age of the patients was 41 years (range 18 to 70 years). Most (72%) were white and most (92%) were women. A total of 41 (22%) patients withdrew from the study (20 [22%] receiving CEP-33457 and 21 [23%] receiving placebo). The most frequent reason for withdrawal was adverse events, which occurred for 10 (11%) patients in the CEP-33457 treatment group and 8 (9%) patients in the placebo group.

Efficacy Results: The SRI at week 24 did not show a statistically significant difference between the CEP-33457 and placebo treatment groups in either the full analysis set or the completer analysis set. Active drug was numerically superior to placebo only at the 8-week time point. Also, none of the secondary or exploratory efficacy variables showed statistically significant differences between the CEP-33457 and placebo treatment groups, except for some isolated cases at specific time points. These isolated numerical differences with small nominal p-values were not considered clinically meaningful.

Safety Results: CEP-33457 was generally safe and well tolerated for up to 48 weeks in patients with SLE. No deaths occurred in this study. The incidence, severity, and types of adverse events reported were similar in the CEP-33457 and placebo treatment groups. The most frequently occurring adverse events (SLE rash, SLE, arthritis, and arthralgia) were likely due to SLE, as skin and musculoskeletal disorders are common in SLE. In both treatment groups, most adverse events were reported as mild or moderate, and severe adverse events occurred with the same frequency (11% of patients in each group). One life-threatening adverse event (seizure, resolved) occurred in the placebo group. The most frequently occurring adverse events considered related to study drug were nausea (5% for patients treated with CEP-33457 and 2% for placebo), and mild injection site erythema (8% for CEP-33457, none for placebo). Serious adverse events were reported for 10% of patients receiving CEP-33457 and 14% of patients receiving placebo. Many of these could be directly attributed to SLE (SLE musculoskeletal symptoms, lupus nephritis, and SLE rash). Others may also represent SLE symptoms, which can manifest as neurologic symptoms, thromboembolic events, and a decreased resistance to many infections. During the

study, 11% of those who received CEP-33457 and 9% who received placebo withdrew because of adverse events. Approximately half of the patient withdrawals may have been related to underlying SLE. The most common adverse events leading to withdrawal were nausea and SLE. For serum chemistry, hematologic variables, urinalysis laboratory tests, and for vital signs and body weight, the results were similar in the 2 treatment groups and there were no clinically important findings at any time point. The ECG abnormalities noted were not marked and reflected changes, such as conduction abnormalities, that occur in a population with SLE.

Pharmacokinetics Results: Blood samples were taken from 19 patients, 8 in the CEP-33457 group and 11 in the placebo group, for measuring plasma concentrations of CEP-33457. The results for all 8 individuals receiving CEP-33457 were either below the limit of quantitation (n=3) or not reportable (n=5). In those "not reportable," the sample viscosity increased so that aliquots could not be taken for sample analysis. This had not occurred previously with quality control samples.

Immunogenicity Results: Two of the 183 patients with blood samples taken had specific anti-CEP-33457 Abs (1 at week 24 and 1 at week 48). The patients with positive titers did not exhibit any clinically significant findings compared with patients with nonreactive titers (ie, there was no marked worsening of SLE, and no allergic or anaphylactic adverse events that would indicate a clinically significant immune response to CEP-33457).

Conclusions: A 200-mcg dose of CEP-33457 given to patients with SLE sc every 4 weeks up to 24 weeks did not demonstrate any efficacy compared with the placebo treatment group in the primary, secondary, or exploratory efficacy variables. The safety data presented indicate that treatment with 200 mcg of CEP-33457 given at 4-week intervals was generally safe and well tolerated for up to 48 weeks in patients with SLE. No new safety signals were identified. The most frequently occurring adverse events were most likely due to the underlying disease.