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: An Open-Label Long-Term Study of the Safety and Tolerability of Repeated Administration of CEP-33457 in Patients With Systemic Lupus Erythematosus

Investigators and Study Centers: The study was conducted at 45 centers in the United States and Europe by 45 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: 09 December 2010 to 14 June 2012 **Phase of Development:** 3

Primary Objective: The primary objective of study CEP-33457/3075 was to evaluate the long-term safety and tolerability of repeated administration of subcutaneous (sc) CEP-33457 every 4 weeks over 72 weeks in patients with systemic lupus erythematosus (SLE) who had participated in a previous Cephalon-sponsored clinical study of CEP-33457. Safety was assessed by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory tests (serum chemistry, hematology, and urinalysis) at each visit during the treatment period
- vital signs (systolic and diastolic blood pressures, pulse, temperature, and body weight) measurements at each visit during the treatment period
- 12-lead electrocardiography (ECG) at the week 48 visit and the final assessment (or early termination)
- physical examination findings, including physical examination symptom-directed findings, at selected time points throughout the study
- concomitant medication usage throughout the study

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

- proportion of patients achieving a clinical response, using the SLE responder index (SRI) at each visit during the treatment period. 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 Physician's Global Assessment (PhGA) (with worsening defined as an increase in PhGA of more than 0.30 points from baseline), no British Isles Lupus Assessment Group A (BILAG A) organ domain score, and no more than 1 new BILAG B organ domain score from baseline.
- change in SLEDAI-2K score at each visit during the treatment period
- change in BILAG-2004 score at each visit during the treatment period
- the effect of CEP-33457 on the status of disease (PhGA) at each visit during the treatment period
- the effect of CEP-33457 on the status of disease (Patient's Global Assessment [PtGA] scale) at visits at weeks 12, 24, 36, 48, and 60 and the final assessment (or early termination)
- 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 visits at weeks 12, 24, 36, 48, and 60 and the final assessment (or early termination)
- 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 visits at weeks 12, 24, 36, 48, and 60 and the final assessment (or early termination):
  - anti–U1 ribonucleoprotein antibody (anti-U1RNP Ab)
  - anti-Smith antibody (anti-Sm Ab)
  - C-reactive protein (CRP)
  - immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin E (IgE)
  - antinuclear antibody (ANA)
- the effect of CEP-33457 on the incidence of disease flares, eg, Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) Flare Index 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 (SLICC/ACR) Damage Index at visits at weeks 24 and 48 and the final assessment (or early termination)
- remission of disease (ie, reduction of SLEDAI-2K score to 0)
- proportion of patients with changes in steroid dose over time throughout the study

The immunogenicity of CEP-33457 was assessed by the following:

- any presence of anti–CEP-33457 antibodies (Abs) at the weeks 24 and 48 visits and the final assessment (or early termination)

Number of Patients (Planned and Analyzed): The planned enrollment for this study was 130 patients. Data from 136 patients were analyzed for efficacy and 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 completed at least visit 8 (week 24) in the Cephalon-sponsored clinical study CEP-33457/2047. 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 American College of Rheumatology (ACR) Classification Revised Criteria. Women must have been surgically sterile, 2 years postmenopausal, or using contraception. The patient had to be willing and able to comply with study procedures.

Main Criteria for Exclusion: Patients were to be excluded from this study if 1 or more of the following main criteria were met (not all inclusive): If they had congestive heart failure, an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2, specified liver function test abnormalities, clinically significant abnormalities on the 12-lead ECG not related to SLE, a history of alcohol or substance dependence or abuse, an ongoing active systemic infection requiring treatment, or a severe infection in the 3 months before the first dose of study drug. Pregnant and lactating women were also excluded. Other exclusion criteria were a history of a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, antibodies to human immunodeficiency virus (HIV) or HIV disease, and a history of severe allergic reactions to or hypersensitivity to any component of the study drug.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: 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 injection. Patients received 200 mcg sc of CEP-33457 every 4 weeks, for a maximum number of 18 doses. The CEP-33457 lot numbers were 09DD003A503, 10-000963, 11-000452.

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

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: This study had a baseline visit, a 68-week treatment period with visits every 4 weeks, and a final assessment 4 weeks after the last dose of study drug. Patients could participate in the study for up to approximately 72 weeks.

General Design and Methodology: This open-label study only enrolled patients who had completed at least through visit 8 (week 24) in study CEP-33457/2047, which was a randomized, double-blind, placebo-controlled study of CEP-33457. The baseline visit for this study was the same as the final assessment visit for study CEP-33457/2047 and had to occur on the same day (±7 days from the previous visit in study CEP-33457/2047). Results from the final assessments in study CEP-33457/2047 were used as baseline data for this study. These assessments included the physical examination and tests to determine health status; assessments of disease and disease activity, such as the SLEDAI-2K, BILAG-2004,

SELENA Flare Index, SLICC/ACR Damage Index, SF-36, PhGA, PtGA, and biologic markers of disease; any presence of anti-CEP-33457 Abs; and safety assessments. Patients who completed the 68-week treatment period were to return to the study center at week 72 for final procedures and assessments. Patients withdrawn from the study before completing all scheduled assessments were to have final procedures and assessments performed within 28 (±7) days of the last study drug administration. Patients withdrawn from the study because of toxicity (including severe flare) were to be monitored for safety until the adverse event resolved or stabilized.

Efficacy Measures and Endpoints: The efficacy variables and endpoints for this study were as follows:

- proportion of patients achieving a clinical response using the SRI at each visit during the treatment period. An SRI response was defined as a reduction from baseline in the SLEDAI-2K score of at least 4 points, no worsening in PhGA (with worsening defined as an increase in PhGA of more than 0.30 point from baseline), no BILAG A organ domain score, and no more than 1 new BILAG B organ domain score from baseline.
- change in SLEDAI-2K score at each visit during the treatment period
- change in BILAG-2004 score at each visit during the treatment period
- the effect of CEP-33457 on the status of disease (PhGA) at each visit during the treatment period
- the effect of CEP-33457 on the status of disease (PtGA) at weeks 12, 24, 36, 48, and 60 and the final assessment (or early termination)
- the effect of CEP-33457 on health-related quality of life, as assessed by completion of the SF-36 at weeks 12, 24, 36, 48, and 60 and the final assessment (or early termination)
- the effect of CEP-33457 on the following biologic markers of disease activity at each visit during the treatment period:
  - anti-dsDNA Ab
  - C3 and C4
- the effect of CEP-33457 on the following biologic markers of disease activity at weeks 12, 24, 36, 48, and 60 and the final assessment (or early termination):
  - anti-U1RNP Ab
  - anti-Sm Ab
  - CRP
  - IgG, IgM, and IgE
  - ANA
- the effect of CEP-33457 on the incidence of disease flares, eg, SELENA Flare Index at each visit during the treatment period
- the effect of CEP-33457 on the occurrence of SLE-induced organ damage, eg, SLICC/ACR Damage Index at weeks 24 and 48 and the final assessment (or early termination)
- remission of disease (ie, reduction of SLEDAI-2K score to 0)
- proportion of patients with changes in steroid dose over time throughout the study

Immunogenicity was assessed by determining the presence of any anti-CEP-33457 Abs.

Safety Variables: The safety and tolerability of CEP-33457 were assessed throughout the study 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 (blood pressure and pulse) and body weight measurements, 12-lead ECG results, physical examination results (including symptom-directed findings), and concomitant medication usage. In addition, an independent, external Data and Safety Monitoring Board oversaw the safety of the patients and monitored the occurrence of any flares throughout the study.

Pharmacokinetics: Pharmacokinetics were not assessed in this study.

Statistical Considerations: Enrolled patients included all those enrolled in the study, whether or not they took study drug. Enrolled patients who took at least 1 dose of study drug were included in the safety analyses and in the intent-to-treat efficacy analyses. At least 130 patients were expected to be enrolled into this study after completing at least up to visit 8 (week 24) in study CEP-33457/2047. This estimated enrollment assumed that approximately 160 (200 × 80%) participants in study CEP-33457/2047 would qualify for this study and that approximately 130 of those who qualified (160 × 80%) would continue in this study. Results are presented for the total open-label population in this study, and for the total

population divided based on the randomized double-blind treatment received during study CEP-33457/2047 (200 mcg sc CEP-33457 or placebo every 4 weeks). All efficacy variables were summarized by time point. The SRI, SLEDAI-2K, BILAG-2004, PhGA, PtGA, SF-36, SELENA Flare Index, SLICC/ACR Damage Index, and biomarker results were summarized using descriptive statistics. For continuous variables, the summary statistics included number, mean, standard deviation, standard error, median, minimum, and maximum. For categorical variables, counts and percentages are provided. Categories for missing data are presented if necessary.

Summary of Results

Patient Disposition and Demography: All 136 enrolled patients received at least 1 dose of study drug and were evaluable for safety and efficacy. There were 135 (>99%) patients withdrawn from the study because the study was closed by the sponsor before completion (no safety issues involved, the closure was for business reasons). The most frequent reason for withdrawal was "other." Of the 110 (81%) patients withdrawn for other reasons, 107 patients were withdrawn because of the study termination. The other 3 patients withdrawn for other reasons took concomitant medications that exceeded the allowable steroid dose limit. The average age of the patients was 40.6 years (range, 18.0 to 70.0 years). Most (74%) of the patients were white, and most (91%) were women.

Efficacy Results: Although evaluation of efficacy was not a primary objective in this study, efficacy was measured with various assessments and no evidence of efficacy was observed. The results of the SRI and SLEDAI-2K showed that peak response rates (around week 20) were below 20% and decreased over time. The proportion of patients with a BILAG-2004 response (no new A body system score and no more than 1 new B body system score from baseline) generally decreased during the study. The proportion of patients with no worsening on the PhGA and PtGA scales generally declined during the treatment period also and only small changes occurred in the patients' quality of life, based on the SF-36. There were no marked differences in responses between those who received CEP-33457 and those who received placebo in study CEP-33457/2047. Samples taken from 126 patients to measure the presence or absence of specific anti-CEP-33457 Abs showed that 9 patients had postdose reactive titers; however, there was no indication of any impact on safety (no marked worsening of SLE, and no allergic or anaphylactic adverse events). Any fluctuations in disease activity over time were likely due to SLE, a disease that is characterized by remissions and exacerbations.

Safety Results: Most (55%) patients received 5 to 8 injections of CEP-33457 and the maximum number of days of exposure was 450 days (approximately 64 weeks). The safety data indicated that 200 mcg sc of CEP-33457 given at 4-week intervals was generally safe and well tolerated. There were no deaths, and overall, the incidence, severity, and types of adverse events reported were similar to those reported in study CEP-33457/2047. At least 1 adverse event was reported by 86% of patients in this study. The organ systems most frequently involved were infections and infestations, musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders. The most frequent specific adverse events included upper respiratory tract infection and adverse events due to the underlying disease, such as SLE and SLE rash. Most adverse events were categorized as mild or moderate in severity. The most frequently occurring adverse events considered related to study drug treatment were injection site erythema, nausea, bronchitis, and pneumonia, each of which occurred in 3 (2%) patients. All of the treatment-related injection site adverse reactions (pruritus, erythema, and site swelling) were mild. Eleven (8%) patients had serious adverse events, most of which were likely due to underlying SLE and were not considered related to study drug. Nine (7%) patients were withdrawn from the study because of adverse events; the most frequent reason for withdrawal was worsening SLE or SLE flare. No differences were observed in this study between those who had received CEP-33457 and those who had received placebo in study CEP-33457/2047. There were no clinically important findings in serum chemistry, hematologic variables, urinalysis laboratory tests, or in vital signs and body weight. The ECG abnormalities noted were not marked and reflected changes, such as conduction abnormalities, that occur in a population with SLE.

Conclusions: In this study, 200 mcg of CEP-33457 given every 4 weeks for up to 64 weeks (64 weeks because the study was terminated) did not demonstrate any efficacy in reducing SLE-related symptoms. The safety data indicated that the above dosage of CEP-33457 was generally safe and well tolerated for up to 64 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.