2. SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceutical Industries Ltd.	**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: Laquinimod capsules		
Name of Active Ingredient: Laquinimod	**Volume:**	
	Reference:	

Title of Study: A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Clinical Effect of Laquinimod in Active Lupus Nephritis Patients, in Combination with Standard of Care (Mycophenolate Mofetil and Steroids)

Investigators and Study Centers: The study was conducted at 16 centers by 16 investigators in 4 countries. A complete list of investigators and their affiliations is included in the clinical study report.

Publication (reference): At the time of approval of this report, results from this study had been published:

Jayne D, Appel G, Chan TM, Barkay H, Weiss R, Wofsy D. A randomized controlled study of laquinimod in active lupus nephritis patients in combination with standard of care [abstract]. Ann Rheum Dis 2013;72(Suppl 3):164.

Study Period: 01 September 2010 to 24 October 2012 **Phase of Development:** 2a

Objectives: The objectives of this exploratory study were to evaluate the safety, tolerability, clinical effects, and effects on biomarkers of 2 doses of laquinimod (0.5 and 1 mg/day) compared with placebo in patients with active lupus nephritis (LN) in combination with standard of care treatments (mycophenolate mofetil [MMF] and steroids).

Number of Patients (Planned and Analyzed): 45 patients were planned to be enrolled, 15 in each treatment group; data from 46 patients were analyzed for efficacy and safety; 29 patients had pharmacokinetic data for laquinimod and 42 patients had pharmacokinetic data for mycophenolic acid (MPA), the active metabolite of MMF, at week 4.

Diagnosis and Main Criteria for Inclusion: Patients were included if all of the following main criteria were met (not all inclusive): The patient was a man or woman between 18 and 75 years of age with systemic lupus erythematosus (SLE), who met at least 4 SLE criteria as defined by the American College of Rheumatology (ACR) Classification Revised Criteria, and had a positive test for anti-nuclear antibodies (ANA) or a positive test for anti-double-stranded deoxyribonucleic acid antibodies (anti-dsDNA Abs) between screening and baseline. They must have had a diagnosis of LN, with a kidney biopsy within 12 months before baseline, and histopathological evidence of glomerulonephritis (diagnosis of proliferative and/or membranous LN; International Society of Pathology/Renal Pathology Society III [A or A/C], IV-S or IV-G [A or A/C], or class V, either pure or in combination with class III or IV). Patients were to have clinically active LN as evident by a urine protein-to-creatinine ratio (UPCR) of 1 or higher, for LN classes III, IV, or class V in combination with classes III or IV, or a UPCR of 2 or higher for LN class V at screening or between screening and baseline.

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): had an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2 or below; had a planned or previous kidney transplant; or received dialysis within the last month before screening or were scheduled to receive dialysis. Also excluded were patients with severe, unstable, or progressive central nervous system lupus and/or associated with significant cognitive impairment, and those with clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation. Pregnant and lactating women were excluded. Laboratory test results that would exclude patients at screening were serum elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, or low levels of hemoglobin, neutrophils, or platelets. There were specified restrictions regarding dosages of MMF, corticosteroids, and immunosuppressive drugs previously taken.

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

Investigational Product: Laquinimod 0.5-mg capsules (batch number K-44082). All patients took 2 capsules orally, either 1 laquinimod 0.5-mg capsule and 1 matching placebo capsule, or 2 laquinimod 0.5-mg capsules.

Placebo: Patients in the placebo group took 2 placebo capsules per day (batch number K-44094).

Additional Drugs: All patients received marketed 500-mg MMF tablets (batch numbers 13M055 and 30208235) provided by Teva. MMF treatment started at 500 mg twice daily (bid) for the 1st week and increased to 1 g bid in the 2nd week and throughout the study. Some dosage adjustments could be made for patients already taking MMF before baseline, for lack of efficacy, or for intolerance to MMF. All patients were also to receive 500 mg/day intravenous methylprednisolone at the site on days 1 through 3, followed by 40 mg/day of oral prednisone/prednisolone, which was to be tapered down according to a predefined tapering scheme. Some steroid dosage adjustments could be made. By the end of week 20, the prednisolone/prednisone was to be tapered to 10 mg/day or less, and thereafter patients were to maintain a stable steroid dose (defined as <5 mg change in prednisone/prednisolone dose from the week 20 dose).

Method of Blinding: At baseline, a dynamic randomization using a minimization algorithm was used to assign patients to 0.5 mg/day laquinimod or placebo in a 1:1 ratio. After the Safety Committee reviewed data from at least 10 patients who had completed at least 4 weeks of treatment, and approved continuation of the study, enrollment into the laquinimod 1-mg dose group was initiated. Patients were then assigned to 0.5 mg/day laquinimod, 1 mg/day laquinimod, or placebo in a ratio that allowed reaching a target enrollment of approximately 15 patients per treatment group. The algorithm had 3 stratification factors: estimated glomerular filtration rate (eGFR) of ≥60 or <60 mL/min/1.73 m^2; UPCR of >3 or ≤3; and region (United States and Canada; France and United Kingdom; Russia). An interactive voice/web response system was to assign treatments.

Duration of Treatment: This study had a screening period up to 4 weeks, a laquinimod/placebo treatment period of 24 weeks, and a final assessment done at week 28, or 4 weeks after the last dose of study drug. Treatment with MMF began at baseline and continued until week 28 and steroid dosages were as described above.

General Design and Methodology: This was a randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and clinical effects of laquinimod in combination with MMF and steroids in patients with active LN. Clinic visits were conducted at screening, baseline, days 2 and 3, and weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24, and a follow-up visit was scheduled at week 28.

Efficacy Measures and Endpoint(s): This was an exploratory study with no formal hypothesis testing planned. The LN-related measures included the eGFR, serum creatinine levels, total urine protein, UPCR, and composite renal responses based on eGFR, serum creatinine, and UPCR. Assessments of general SLE disease activity were made using the British Isles Lupus Assessment Group (BILAG) 2004, the physician global assessment (PGA), and the patient global assessment (PtGA). Disease control was evaluated based on oral steroid dose reduction by week 20 and lack of disease flare. The immunologic markers measured for SLE were anti-dsDNA Abs, complement components C3, C4, CH50 and anti-C1q, and the direct Coombs test. Results from the biomarker analyses will be analyzed and provided in a separate report.

Safety Variables: Safety assessments included evaluations of adverse events (including deaths, serious adverse events, and withdrawals due to adverse events), clinical laboratory tests (serum chemistry, hematology, and urinalysis), vital signs (blood pressure and pulse), electrocardiogram results, and concomitant medication usage.

Pharmacokinetics: Blood samples for pharmacokinetic evaluation of laquinimod and MPA, were collected from all patients at week 4 before study drug was administered, and then after study drug at the following time points: 15 and 30 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours. Blood samples were taken before study drug was administered to obtain trough plasma levels of laquinimod and MPA at weeks 12 and 24, and to obtain trough plasma levels of MPA at week 28.

Statistical Considerations: After the final protocol amendment, changes were made in the statistical methods. Details were described in the statistical analysis plan and additional changes, made before unblinding the treatments, were documented in the blinded data review meeting (BDRM) minutes. The intent-to-treat (ITT) analysis set included all patients as randomly assigned to treatment. The modified intent-to-treat (mITT) analysis set (leading set) had all patients in the ITT population, excluding observations after treatment failure. The per-protocol (PP) analysis set included all patients who completed the treatment period (24 weeks) and had no major protocol violations during the treatment period. The safety (ST) analysis set included all randomly assigned patients who received at least 1 dose of study drug. Descriptive statistics and the percentage changes from baseline were tabulated by visit and treatment group for eGFR, serum creatinine levels, total urine protein (24-hour and spot), UPCR (24-hour and spot), BILAG scores, PGA, PtGA, and SLE immunologic markers. The eGFR was calculated using the Modification of Diet in Renal Disease formula. Four categories of composite renal responses were defined: renal response A, renal response B, and complete and partial renal responses. The proportions of patients with renal responses were tabulated by visit and treatment group. Logistic regression (using SAS® PROC GENMOD, specifying the Binomial distribution and a LOGIT link function) was performed to assess the treatment effect on the

proportion of patients with renal responses at week 24. Treatment group was a categorical variable. The model included race as a covariate. The confidence intervals for the odds ratio between each laquinimod group and placebo, and the adjusted proportion for each treatment group, are presented.

Summary of Results

Patient Disposition and Demography: A total of 82 patients with LN were screened for this study; 46 patients were enrolled; all 46 patients were evaluated for safety and efficacy; and 42 patients completed 24 weeks in the study. Four (8.7%) patients withdrew from the study, 2 (13.3%) receiving 1 mg/day laquinimod withdrew due to adverse events and 2 (13.3%) receiving placebo withdrew due to lack of efficacy. The demographics were generally similar in the 3 treatment groups. The total population mean age was 33.8 years and ages ranged from 18.3 to 71.6 years old. More patients were women (34, 73.9%) than men (12, 26.1%). Of the 46 patients, 27 (58.7%) were white, 8 (17.4%) were black, 7 (15.2%) were Hispanic, 3 (6.5%) were Asians, and 1 was categorized as other. The baseline characteristics differed; more patients in the placebo group had normal eGFRs, and the 3 patients with severe renal insufficiency were in the laquinimod groups, suggesting those assigned to the laquinimod groups may have had more severe illness.

Efficacy Results: There appears to be a trend toward greater improvement in the laquinimod groups than in the placebo group. The eGFR mean percentage changes from baseline were 18.0% in the 0.5-mg laquinimod group, 24.3% in the 1-mg laquinimod group, and 12.1% in the placebo group at week 24/early termination. Greater decreases in spot UPCR and 24-hour UPCR were observed with laquinimod than with placebo. For the spot UPCR, mean percentage changes from baseline to week 24/early termination were –61.4% ±22.81% in the 0.5-mg laquinimod group, –23.0% ±53.59% in the 1-mg laquinimod group, and –8.3% ±81.26% in the placebo group. The mean percentage changes in spot UPCR were lower for both laquinimod groups than for placebo at all time points after week 1. The 24-hour UPCR results were consistent with the spot UPCR results. When renal response A criteria were calculated based on spot UPCR, there was a greater proportion of responders at week 24 in both laquinimod groups than in the placebo group and response rates were maintained over all time points from week 8 forward in the laquinimod 0.5-mg group compared with the placebo group. The results for renal response A criteria based on 24-hour UPCR were consistent with the spot urine results. Renal response B and the complete renal response required a UPCR below 0.5, which would be difficult to attain within 6 months of starting treatment. No differences among treatment groups were seen for renal response B. Analysis of the complete and partial renal responses based on spot UPCR showed a slightly better response in the 0.5-mg laquinimod group than either the placebo or 1-mg laquinimod groups, although the numbers for complete renal response were very small. There were no marked changes in the total BILAG score. Of the changes in the BILAG body system scores, the greatest improvement in renal system scores occurred in the 0.5-mg laquinimod treatment group. All 16 (100%) patients in this group had renal A scores (severe) at baseline; by week 24, only 4 (25%) patients in this group had renal A scores. In the 1-mg laquinimod treatment group, 11 (78.6%) patients had renal A scores at baseline and 6 (40%) patients had renal A scores at week 24. In the placebo group, 11 (73.3%) patients had renal A scores at baseline and 6 (40%) patients had renal A scores at week 24. The PGA scores at week 24 showed greater reductions from baseline in the laquinimod-treated groups than in the placebo group. No differences between treatment groups were seen in the PtGA scores. Most patients were also able to reduce their oral steroid doses with no SLE flare. The C3 and C4 levels changed from abnormal at baseline to normal at week 24 in greater proportions of patients treated with laquinimod than in placebo-treated patients.

Safety Results: During the study, 93.8%, 100%, and 93.3% of the patients in the 0.5-mg laquinimod, 1-mg laquinimod, and placebo groups, respectively, reported at least 1 adverse event. The most common adverse events were infections and infestations and gastrointestinal disorders. Of the 29 patients with infections and infestations, 8 (50.0%) were in the 0.5-mg laquinimod group, 10 (66.7%) were in the 1-mg laquinimod group, and 11 (73.3%) were in the placebo group. Of the 20 patients with gastrointestinal disorders, 8 (50.0%) were in the 0.5-mg laquinimod group, 6 (40.0%) were in the 1-mg laquinimod group, and 6 (40.0%) were in the placebo group. The overall incidence of infection was not higher in the laquinimod groups. Herpes infections were reported for 1 (6.3%) patient in the 0.5-mg laquinimod group, 4 (26.7%) patients in the 1-mg laquinimod group, and 2 (13.3%) patients in the placebo group. Urinary tract infections were reported by 4 (25%), 4 (26.7%), and 1 (6.7%) patients in the 0.5-mg laquinimod, 1-mg laquinimod, and placebo groups, respectively. Upper respiratory tract infections were reported by 4 (25%), 2 (13.3%), and 5 (33.3%) patients in the 0.5-mg laquinimod, 1-mg laquinimod, and placebo groups, respectively. Fungal infections were not more frequent or severe in laquinimod-treated patients. Gastrointestinal and abdominal pain were reported by 3 (18.8%) patients in the 0.5-mg laquinimod group, 1 (6.7%) patient in the 1-mg laquinimod group, and no patients in the placebo group. Diarrhea occurred in 2 (12.5%) patients in the 0.5 mg/day laquinimod group, 3 (20.0%) patients in the 1 mg/day

laquinimod group, and 1 (6.7%) patient in the placebo group. Abdominal pain and diarrhea have both been reported as adverse events in other laquinimod studies, and are also reported with MMF treatment. Most adverse events for patients in all 3 treatment groups were reported as mild or moderate in severity and severe adverse events occurred in all treatment groups. Twelve patients had serious adverse events, 4 in each treatment group, and 2 patients withdrew due to adverse events. One serious adverse event resulted in death; patient PPD in the 1-mg/day laquinimod group, developed acute tracheobronchitis and bilateral pneumonia on study day 33. Study drug was discontinued on day 41. She then had sepsis including leukopenia, disseminated intravascular coagulation, worsening renal failure, and cardiorespiratory arrest, and died on day 49 of the study. The events were considered possibly related to both laquinimod/placebo and MMF. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) were to be excluded from this study; however, patient PPD was permitted to enroll because 1 of 3 eGFR values was above the criterion for eGFR. Another patient in the 1-mg laquinimod group (patient PPD developed sepsis, which started on day 133 and lasted 11 days; he recovered and was withdrawn from the study. Three patients had vascular serious adverse events. Two of these patients were treated with laquinimod 0.5 mg; patient PPD who developed a deep venous thrombosis and pulmonary embolism, and patient PPD who developed a superficial thrombophlebitis of the minor saphenous vein of the left leg. The 3rd patient (patient PPD treated with placebo, developed a deep venous thrombosis in the left leg. In addition, patient PPD had a serious adverse event of atrial fibrillation associated with an event of pleuritic pain (pulmonary embolism was ruled out). The cardiac and vascular adverse events were considered unrelated to either laquinimod or MMF. Some of the serious adverse events were related to the underlying lupus. There were no clinically meaningful trends in mean changes from baseline or in shifts of any clinical laboratory variable from the normal range at baseline to outside the normal range during the study. No patient met Hy's law criteria for drug-induced liver injury during this study. There were no clinically important changes in vital signs values during this study.

Pharmacokinetics Results: The mean values of laquinimod pharmacokinetic parameters (C_{max}, AUC_{last}, and C_{min}) increased with dose, reaching maximum concentrations between 1 and 2 hours after dose administration on average, and decreasing slowly during the 24-hour interval, which was consistent with the previously reported long terminal phase $t_{½}$ of laquinimod. More variability was observed in the 1-mg than in the 0.5-mg laquinimod group for all 3 parameters. Predose concentrations of laquinimod were quantifiable in all patients at week 4, suggesting systemic accumulation with once daily administration of laquinimod. The predose and the 24-hour concentrations were comparable in both dose groups. Trough concentrations of laquinimod at weeks 4, 12, and 24 were comparable in both treatment groups, suggesting that steady state was likely attained within 4 weeks of once daily administration. A post-hoc analysis of laquinimod pharmacokinetics and renal measures showed no correlation between eGFR level and pharmacokinetic parameters at week 4, suggesting that lower levels of eGFR did not seem to affect laquinimod exposure based on C_{max}, AUC_{last}, or C_{min}.

Conclusions: The results of this study suggest that laquinimod dosages of 0.5 or 1 mg/day taken for up to 6 months with MMF and corticosteroids might be more effective than placebo with MMF and corticosteroids in improving lupus-related nephritis. Pharmacokinetic analyses indicate that laquinimod did not have a clinically meaningful effect on MMF exposure. Also, laquinimod exposure was similar across different categories of renal function, suggesting that there is no requirement for dose adjustment in patients with LN and mild to moderate renal insufficiency. Overall, laquinimod in combination with MMF and corticosteroids was safe and well tolerated in the active LN population studied. Serious adverse events occurred in the same frequency in all treatment groups; 1 death and 1 additional withdrawal due to a serious adverse event (sepsis) occurred in the 1-mg/day laquinimod group. The most common adverse events reported, infections and infestations and gastrointestinal disorders, had generally similar frequencies in the 3 treatment groups. There were no malignancies reported during this study. The overall risk of infection was not higher in the laquinimod groups. No opportunistic infections occurred during the study; there were a small number of nonserious herpes zoster infections in all treatment groups. No patient met Hy's Law criteria for drug-induced liver injury during this study. There were no clinically important changes in weight or vital signs values during this study. Overall, laquinimod at 0.5 and 1 mg/day appears to be well tolerated, although the 0.5-mg/day dosage may have a slightly better risk-benefit profile. This is not a robust conclusion, given the size of the study population and short duration of the study. Nevertheless, the results support further investigation of laquinimod for the treatment of LN.