1 Study Synopsis

<table>
<tr><td>Name of Sponsor/Company:
Glenmark Pharmaceuticals SA</td><td>Individual Study Table Referring to Part of the Dossier</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Investigational Product:
Revamilast</td><td>Volume:</td></tr>
<tr><td>Name of Active Ingredient:
GRC 4039</td><td>Page:</td></tr>
<tr><td colspan="3">Title of Study: A Phase IIb, 12 Week Randomized, Double-blind Parallel Group, Placebo-controlled, Study to Evaluate Efficacy, Safety and Tolerability of 2, 4 and 6 mg of Revamilast in Patients with Active Rheumatoid Arthritis who have had an Inadequate Response to Methotrexate</td></tr>
<tr><td colspan="3">Investigators: Dr. Slawomir Jeka M.D., PhD was the co-ordinating investigator in Poland, Dr. Lalith Wijayaratne M.D. was the co-ordinating investigator in Sri Lanka, and Prof. Paul Emery M.D., FRCP was the co-ordinating investigator in the UK. There was no co-ordinating investigator for India or the Philippines. A list of all investigators is provided in Appendix 16.1.4.</td></tr>
<tr><td colspan="3">Study Centers: Patients were recruited at 42 study centers in 5 countries. Patients were recruited at 24 study centers in India, 7 study centers in Poland, 6 study centers in the Philippines, 4 study centers in Sri Lanka, and at 1 study center in the United Kingdom (UK).</td></tr>
<tr><td colspan="2">Publication (Reference): None</td><td>Phase of Development: IIb</td></tr>
<tr><td colspan="3">Studied Period: 08 Nov 2011 to 20 Dec 2012.</td></tr>
<tr><td colspan="3">Objectives:
Primary
• To determine the efficacy of 4 mg and 6 mg of Revamilast compared to placebo in the treatment of patients with active rheumatoid arthritis (RA) who have had an inadequate response to methotrexate (MTX).
Secondary
• To evaluate the safety and tolerability of Revamilast at 2 mg, 4 mg and 6 mg dose compared to placebo.
• To determine a low precision estimate of the efficacy of 2 mg of Revamilast compared to placebo.
• To investigate the pharmacokinetics (PK) of 2 mg, 4 mg and 6 mg of Revamilast and GRC-4037 in patients with RA (rich PK sampling in 48 patients – 12 patients in each arm, at selected sites with appropriate facility and population PK sampling in all patients including those undergoing rich sampling).
• To investigate the effects of Revamilast on pharmacodynamic (PD) parameters including: serum interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α and serum C-reactive protein (CRP).</td></tr>
<tr><td colspan="3">Methodology: This was an outpatient, multi-center, randomized, double-blind, placebo-controlled, parallel group dose-ranging study in patients with active RA receiving a stable or maximum tolerated dose of MTX for a minimum of 12 weeks before the screening visit (Visit 1) and a stable dose of oral folic acid (≥5 mg/week) that started at least 1 week before the screening visit. A stable dose of oral corticosteroid (equivalent to ≤10 mg/day of prednisone) starting at least 4 weeks before the screening visit and a stable dose of a non-steroidal anti-inflammatory drug (NSAID) or selective</td></tr>
</table>

cyclooxygenase (COX) inhibitor starting 4 weeks before randomization were allowed. After a 4-week, single-blind placebo run-in period, patients were randomized (in a 1:2:2:2 ratio) to receive treatment with Revamilast (2 mg or 4 mg or 6 mg) or placebo for 12 weeks. Paracetamol as rescue medication was allowed during the study (not more than 2.5 g/day [not more than 2.0 g/day for Indian sites] and for not more than 4 consecutive days) during the run-in period, treatment period, and follow-up period). Patients attended a screening visit (Week -5 [Visit 1]), a visit at the start of the run-in period (Week -4 [Visit 2]), an evaluation visit (Week -2 [Visit 3]) 2 weeks after Visit 2, and a randomization visit at the end of the run-in period (Week 0 [Visit 4]). During the treatment period there were 4 further study visits (Weeks 2, 4, 8, and 12 [Visits 5 to 8]), and a follow-up visit 2 weeks after the last treatment visit (Week 14 [Visit 9]). The subset of patients selected for rich PK sampling had an additional time-point scheduled 24 hours (h) after Week 0 (Visit 4) and Week 12 (Visit 8) and 4 days after Week 12 (Visit 8) to complete collection of blood samples for PK analysis. Sparse PK blood samples were to be collected from all patients (including the patients undergoing rich sampling) at pre-dose and 4 h post dose at Week 4 (Visit 6). A patient diary was used to collect some study data.
Number of Patients (Planned and Analyzed): It was intended that 406 patients would be randomized. Sparse PK sampling was to be collected from all randomized patients and rich PK sampling was to be collected from approximately 48 patients (12 patients per treatment arm) selected from the study centers in India only. Although sparse and rich PK samples were collected from patients in all treatment arms, including placebo, only samples from patients in the active treatment arms (ie, 2 mg, 4 mg or 6 mg Revamilast) were analyzed for plasma concentrations of Revamilast and its metabolite. A total of 449 patients entered the single-blind placebo run-in period and 435 patients were randomized in the interactive voice response system (IVRS). Twelve patients were excluded from the randomized population: 11 patients were excluded due to a fire at Study Center 1038 and one patient was excluded due to significant bradycardia. A total of 423 patients were included in the randomized population (125 patients, 57 patients, 122 patients, and 119 patients in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively), 410 patients were included in the safety population (119 patients, 55 patients, 122 patients, and 114 patients in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively), 406 patients were included in the modified intent-to-treat (mITT) population (117 patients, 54 patients, 122 patients, and 113 patients in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively), and 366 patients were included in the efficacy evaluable (EE) population (109 patients, 45 patients, 107 patients, and 105 patients in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively). Rich PK samples from a total of 50 patients in the 2 mg, 4 mg, and 6 mg Revamilast treatment arms (13, 19, and 18 patients, respectively) were analyzed at Week 0 (Visit 4) and rich PK samples from 34 patients (11 patients each in the 2 mg and 6 mg Revamilast treatment arms, and 12 patients in the 4 mg Revamilast treatment arm) were analyzed at Week 12 (Visit 8). Sparse PK samples from 264 patients in the 2 mg, 4 mg, and 6 mg Revamilast treatment arms (53, 108, and 103 patients, respectively) were analyzed at Week 4 (Visit 6).
Diagnosis and Main Criteria for Inclusion: Male or female patients aged 18 to 65 years with a documented history of RA according to the revised (1987) American College of Rheumatology (ACR) criteria for at least 6 months before screening who met ACR functional class I, II, or III, had active RA defined as ≥6 swollen and tender/painful joints at the screening and baseline visits (Visits 1 and 4) and at least 2

of the 3 following criteria: rheumatoid factor positive or anti-cyclic citrullinated peptide (CCP) positive at the screening visit; CRP ≥1.2 times the upper limit of normal (ULN) or erythrocyte sedimentation rate (ESR) >28 mm/h (by the Westergren method) at the screening visit; or morning stiffness lasting >45 minutes for at least 4 weeks before informed consent through screening visit; and had disease activity score-28 (DAS-28) CRP values ≥4.5 at the screening visit. Patients must have been on a stable or maximum tolerated dose of MTX (15 mg/week to 25 mg/week with documented adverse drug reaction at a higher dose or maximum approved dose) for a minimum of 12 weeks before the screening visit and on a stable dose of oral folic acid (≥5 mg/week) that started at least 1 week before the screening visit. A stable dose of oral corticosteroid (equivalent to ≤10 mg/day of prednisone [corrected in Protocol Amendment 4 dated 14 Sep 2011 from equivalent to <10 mg/day]) starting at least 4 weeks before the screening visit and a stable dose of an NSAID or COX inhibitor were allowed. Eligible patients receiving stable doses of hydroxychloroquine (HCQS or sulphasalazine (SSZ) at screening completed wash-out from these drugs during the 4-week placebo run-in.
Test Product, Dose and Mode of Administration, Batch Number: 2 mg, 4 mg, or 6 mg Revamilast tablets administered orally once daily in the morning for 12 weeks. Batch numbers are available on request.
Duration of Treatment: One week screening period, 4-week single blind placebo run-in period, 12-week treatment period, and 2-week follow-up period.
Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo to match study medication administered orally once daily in the morning for 12 weeks. Batch numbers are available on request.
Criteria for Evaluation:
Efficacy: Swollen/tender joint count (66/68), patient's assessment of arthritis pain, patient's global assessment of arthritis, physician's global assessment of arthritis, health assessment questionnaire–disability index (HAQ-DI), DAS-28 CRP assessments, levels of the acute phase reactants CRP and ESR, and the use of rescue medication (paracetamol). The ACR definition for calculating improvement in RA is the ACR responder criteria. A patient is an ACR20 responder if the counts for both tender and swollen joints reduce by 20% or more from baseline and 3 of the following 5 assessments show a reduction of 20% or more from baseline: patient's assessment of arthritis pain (visual analogue scale [VAS]), patient's global assessment of arthritis (VAS), physician's global assessment of arthritis (VAS), HAQ-DI, and levels of an acute phase reactant, either CRP or ESR. ACR50 and ACR70 improvement in RA are calculated in the same way as ACR20, with the respective percent improvements.
Safety: Physical examination (including body weight), vital signs, electrocardiogram (ECG) monitoring, clinical laboratory tests, including stool examination for occult blood, adverse events (AEs) including diarrhea monitoring, concomitant medication, and menstrual period monitoring.
Pharmacokinetics: Sparse plasma sampling for PK analysis of Revamilast and its metabolite GRC 4037 was to be performed for all patients at Week 4 (pre-dose and at 4 h post dose). In addition, rich plasma sampling for the PK analysis of Revamilast and its metabolite GRC 4037 from a subgroup of patients from the centers in India only was to be carried out at Week 0 (pre-dose and up to 24 h post dose) and Week 12 (pre-dose and up to 102 h post dose). Plasma concentrations of MTX were also estimated from the rich and sparse plasma samples obtained from patients enrolled at study centers in India only.

Pharmacodynamics: IL-1, IL-6, and TNF-α in blood were analyzed in all patients at Week 0 and at Week 12. ESR and CRP were analyzed in all patients at Week -5 and from Week 0 to Week 14.

Statistical Methods: The primary efficacy endpoint was the percentage of patients in 4 mg and 6 mg Revamilast arms achieving an ACR20 response at 12 weeks relative to placebo. The percentage of patients achieving an ACR20 response at Week 12 was analyzed by Cochran-Mantel-Haenszel chi-square testing, incorporating the baseline stratification factor of investigator center, separately for each pair-wise treatment comparison with placebo, for the mITT and EE populations. The difference in proportions amongst each active treatment group and placebo group and its 95% confidence intervals (CIs) were presented. The level of significance was set to 5% for the inferential tests. The p-values were reported for the pair-wise comparison. No adjustments were made for multiplicity.

The secondary efficacy endpoints were percentage of patients in the 4 mg and 6 mg Revamilast arms achieving an ACR20 response at 4 and 8 weeks of treatment; percentage of patients in the 4 mg and 6 mg Revamilast arms with ACR50 and ACR70 responses at 4, 8, and 12 weeks of treatment; percentage of patients in the 2 mg Revamilast arm achieving ACR20, ACR50 and ACR70 responses at 4, 8, and 12 weeks of treatment; change in DAS-28 CRP from baseline to Week 12 in the 2 mg, 4 mg, and 6 mg Revamilast arms; change from baseline in serum CRP and ESR values in the 2 mg, 4 mg, and 6 mg Revamilast arms; to assess the PD effect of 2 mg, 4 mg, and 6 mg of Revamilast, and frequency and use of rescue medication (paracetamol).

The secondary efficacy endpoints measuring ACR improvement were analyzed in the same way as the primary efficacy endpoint. The observed DAS-28 CRP scores and change from baseline in DAS-28 CRP scores at Week 12 were summarized for the mITT and EE populations. An analysis of covariance (ANCOVA) was used to test for differences in treatment using change from baseline as the dependent variable, treatment as the main effect and stratification factor as investigator center, and baseline value as covariate. For the mITT and EE populations, each component score of the ACR and their change from baseline values were summarized. The change from baseline was analyzed using an ANCOVA with factors for treatment, and stratification factor of investigator center and baseline value as covariate. Estimated differences and 95% CIs were presented for each pair-wise change from baseline difference using a paired t-test between each post baseline visit for each study treatment. The change and percentage change from baseline in ESR and CRP were summarized. Mean differences between each active treatment group's mean change from baseline were estimated along with a 95% CI. The change in values from Week 0 was summarized. Within treatment group differences were tested using a paired t-test. Actual values and percentage change from baseline values were summarized and the change from baseline was also analyzed using an ANCOVA with factors for treatment and investigator center and baseline value as covariate. Estimated differences and 95% CI were presented for each pair-wise difference.

Efficacy analyses were supplemented by imputing missing values using the last observation carried forward (LOCF) methodology for the mITT and EE populations.

Descriptive statistics for the rescue medication dose at each visit and for the entire treatment period were summarized. Additionally, summarization was done by the counts and percentages for the patients who did not meet the compliance criteria of intake of not more than 2.5 g/day (2.0 g/day for India sites) and for not more than 4 consecutive days.

Safety was assessed through vital signs, physical examination, body weight, menstrual cycle, 12 lead ECG, and laboratory parameters, and assessment of AEs and serious adverse events (SAEs), including AEs of special interest (menstrual irregularities, diarrhea, and occult blood). Descriptive statistics were presented for all safety assessment data and changes from baseline were summarized for vital signs, body weight, and laboratory parameters. Change from baseline in vital signs data were analyzed using an ANCOVA with factors for treatment and stratification factor of investigator center and baseline factor as a covariate. Estimated least square means and 95% CIs were presented for change from baseline for each study treatment. ECG abnormality findings observed to be clinically significant were compared for proportion of patients using Cochran-Mantel-Haenszel chi-square testing, incorporating the baseline stratification factor of investigator center, separately for each pair-wise treatment comparison with placebo, for the safety population for Week 14. Based on abnormal physical examination findings observed to be significant, the proportion of patients between placebo and the active dose group were compared using Cochran-Mantel-Haenszel chi-square testing, incorporating the baseline stratification factor of investigator center, separately for each pair wise treatment comparison with placebo, for the safety population.

The PK parameters C_{max}, AUC_{0-t}, $AUC_{0-\tau}$, $AUC_{0-\infty}$, T_{max}, λ_z (lambda z), $t_{½}$, AUC_%Extrap_obs, R^2, metabolite/drug ratio, and T_{last} were reported for Revamilast (GRC 4039) and its metabolite (GRC 4037). For MTX, only the plasma concentrations were reported.

The pharmacodynamic markers of inflammation IL-1, IL-6, TNF-α, ESR, and CRP were analyzed as described as part of the secondary endpoint evaluation described for ESR and CRP.

Summary – Conclusions:

Efficacy Results: There was no statistically significant difference in the percentage of patients in the 2 mg, 4 mg, and 6 mg Revamilast treatment arms achieving an ACR20 response at Week 4, Week 8, or Week 12 relative to placebo for the mITT or EE populations when the analysis was performed with or without LOCF methodology.

The percentage of ACR20 responders increased at each visit up to Week 12 in all treatment arms (46 patients [39.3%], 26 patients [48.1%], 53 patients [43.4%], and 43 patients [38.1%], respectively, for the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms for the mITT population with LOCF at Week 12).

The best reported ACR50 response in any treatment arm at Week 12 was 9 patients (16.7%) in the 2 mg Revamilast treatment arm for the mITT population with LOCF. In the same population with LOCF at the same time-point, 10 patients (8.5%), 11 patients (9.0%), and 9 patients (8.0%) achieved an ACR50 response in the placebo and 4 mg and 6 mg Revamilast treatment arms, respectively. The best reported ACR70 response in any treatment arm at Week 12 was 4 patients (3.5%) in the 6 mg Revamilast treatment arm for the mITT population with LOCF. In the same population with LOCF at the same time-point, 1 patient (0.9%), 0 patients, and 2 patients (1.6%) achieved an ACR70 response in the placebo and 2 mg and 4 mg Revamilast treatment arms, respectively.

There was no statistically significant difference in the 2 mg, 4 mg, or 6 mg Revamilast treatment arms in change from baseline in DAS-28 CRP at Week 12 relative to placebo for the mITT or EE populations when the analysis was performed with or without LOCF methodology. The only exception was for the 4 mg Revamilast treatment arm, where the analysis without LOCF in the mITT and EE populations ($p = 0.0075$ and $p = 0.0171$, respectively) showed a statistically significant difference in favor of placebo. The mean

(standard deviation [SD]) change from baseline for the mITT population with LOCF methodology was 0.95 (9.864) for placebo and 2.25 (8.883), -0.26 (6.723), and 1.47 (5.151) for the 2 mg, 4 mg, and 6 mg Revamilast treatment arms. Positive values represent an improvement from baseline. The mean (SD) change from baseline for the mITT population without LOCF methodology was 1.03 (0.926) for placebo and 1.07 (0.974), -0.37 (7.041), and 1.61 (5.574) for the 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively.

There was no statistically significant difference in change from baseline in CRP between the 2 mg, 4 mg, and 6 mg Revamilast treatment arms compared with placebo at any time-point when the analysis was performed with or without LOCF for the mITT or EE populations, except at Week 4 for the 4 mg Revamilast treatment arm without LOCF for the mITT population and without LOCF for the EE population ($p = 0.0434$, and $p = 0.0332$, respectively), where the analysis showed a statistically significant difference in favor of placebo. There was no notable change in mean CRP in the placebo or 2 mg, 4 mg, and 6 mg Revamilast treatment arms at Week 12 for the mITT or EE populations with or without LOCF methodology.

There was no statistically significant difference in change from baseline in ESR between the 2 mg, 4 mg, and 6 mg Revamilast treatment arms compared with placebo at any time-point when the analysis was performed with or without LOCF for the mITT or EE populations. The mean (SD) ESR change in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms at Week 12 was 4.2 (16.76) mm/hr, 5.6 (22.11) mm/hr, 5.0 (17.81) mm/hr, and 6.0 (18.35) mm/hr, respectively, for the mITT population with LOCF methodology. The mean (SD) change in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms at Week 12 was 4.5 (17.20) mm/hr, 5.4 (22.64) mm/hr, 5.4 (17.65) mm/hr, and 7.1 (18.33) mm/hr, respectively, for the mITT population without LOCF methodology. There was no notable difference in the EE population results compared with the mITT results. Positive values represent an improvement from baseline.

There was no notable difference among the treatment arms in the mean (SD) number of rescue medication tablets taken or in the mean (SD) daily dose of rescue medication.

The mean (SD) change from baseline in duration of morning stiffness at Week 12 was 17.23 (20.017), 25.94 (29.290), 19.08 (33.049), and 20.63 (24.743) minutes for the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively, for the mITT population with LOCF, and was 20.57 (19.606), 26.15 (27.405), 22.43 (34.516), and 22.49 (26.011) minutes, respectively, for the mITT population without LOCF. There was no notable difference in the EE population results compared with the mITT results. Positive values represent an improvement from baseline.

In summary, although there were improvements in measures of efficacy, the differences between Revamilast and placebo were generally not statistically significant and there were no statistically significant differences in favor of Revamilast.

Safety Results: There was no notable difference among the treatment arms in the percentage of patients with a treatment-emergent adverse event (TEAE) (48 patients [40.3%], 19 patients [34.5%], 52 patients [42.6%], and 44 patients [38.6%] in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively). The most frequently reported TEAEs were diarrhea, pyrexia, urinary tract infection, and arthralgia. There was no notable difference among the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms in the percentage of patients reported with diarrhea (4 patients [3.4%], 3 patients [5.5%], 8 patients [6.6%], and 6 patients [5.3%], respectively), pyrexia (4 patients [3.4%], 2 patients [3.6%], 8 patients [6.6%], and

7 patients [6.1%], respectively), urinary tract infection (2 patients [1.7%], 3 patients [5.5%], 6 patients [4.9%], and 7 patients [6.1%], respectively), or arthralgia (7 patients [5.9%], 1 patient [1.8%], 2 patients [1.6%], and 7 patients [6.1%], respectively).

Patients with a TEAE considered related to study medication were reported more frequently in the placebo and 2 mg and 4 mg Revamilast treatment arms compared with the 6 mg Revamilast treatment arm (16 patients [13.4%], 9 patients [16.4%], 19 patients [15.6%], and 10 patients [8.8%], respectively). The most frequently reported TEAEs considered to be related to study medication were diarrhea, occult blood, and urinary tract infection. The incidence of treatment-related diarrhea was lower in the placebo treatment arm compared with the Revamilast treatment arms (2 patients [1.7%] in the placebo treatment arm compared with 3 patients [5.5%], 6 patients [4.9%], and 4 patients [3.5%] in the 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively). Treatment-related occult blood was reported in 3 patients (2.5%), 0 patients, 1 patient (0.8%), and 2 patients (1.8%) in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively, and treatment-related urinary tract infection was reported in 1 patient (0.8%), 2 patients (3.6%), 2 patients (1.6%), and 1 patient (0.9%) in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively.

Severe TEAEs were reported in 2 patients (1.7%), 0 patients, 4 patients (3.3%), and 4 patients (3.5%) in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively. The most frequently reported severe TEAE was diarrhea, reported in 2 patients (1.6%) and 1 patient (0.9%) in the 4 mg and 6 mg Revamilast treatment arms, respectively.

Serious TEAEs were reported only in the placebo and the 6 mg Revamilast treatment arms (2 patients [1.7%] and 5 patients [4.4%], respectively). The most frequently reported serious TEAE was gastroenteritis, reported in 1 patient (0.8%) in the placebo treatment arm and 1 patient (0.9%) in the 6 mg Revamilast treatment arm. A serious TEAE considered to be related to study medication was reported for 2 patients (1.7%) in the placebo treatment arm (facial paresis and hypertensive crisis in 1 patient and gastroenteritis in 1 patient) and for 2 patients (1.8%) in the 6 mg Revamilast treatment arm (vaginal hemorrhage in 1 patient and hemangioma in 1 patient). No deaths were reported during the study.

There was no notable difference among the placebo and 4 mg and 6 mg Revamilast treatment arms in the percentage of patients with at least 1 TEAE leading to withdrawal/discontinuation (4 patients [3.4%]), 4 patients [3.3%], and 6 patients [5.3%], respectively) and no TEAEs leading to withdrawal/discontinuation were reported in the 2 mg Revamilast treatment arm. The most frequently reported TEAEs leading to withdrawal were diarrhea (1 patient [0.8%], 0 patients, 2 patients [1.6%], and 2 patients [1.8%] in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively) and gastroenteritis (1 patient [0.8%], 0 patients, 0 patients and 1 patient [0.9%] in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively).

The most frequently reported TEAE of special interest was diarrhea. There was no notable difference among the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms in the percentage of patients reported with diarrhea (4 patients [3.4%], 3 patients [5.5%], 8 patients [6.6%], 6 patients [5.3%], respectively). Occult blood was reported in 3 patients (2.5%), 2 patients (1.6%), and 3 patients (2.6%) in the placebo, 4 mg, and 6 mg Revamilast treatment arms, respectively. In addition, polymenorrhea was reported for 1 patient (1.8%) in the 2 mg Revamilast treatment arm, and menorrhagia and vaginal hemorrhage were each reported in 1 patient (0.9%) in the 6 mg Revamilast

treatment arm.
There were no notable mean changes from baseline in hematology, clinical chemistry, urine pH, or stool analysis for occult blood at any time-point in any treatment arm. There was no apparent trend in the statistically significant differences in the adjusted mean change from baseline values for the 2 mg, 4 mg, and 6 mg Revamilast treatment arms relative to placebo at any dose and at any time-point for any of the hematology or clinical chemistry variables. For all hematology and clinical chemistry variables, an abnormal clinically significant result was reported in a maximum of 2 patients in any treatment-arm at any post-baseline time-point. No abnormal clinically significant values were reported for urine pH at any time-point. Although a number of shifts from normal at baseline to low or high at post-baseline time-points were reported for >10% of patients for hematology or clinical chemistry results, none were considered clinically significant. No individual patient hematology or clinical chemistry abnormalities were considered to be an SAE or an AE leading to withdrawal. Proteinuria was reported as an AE leading to withdrawal for 1 patient in the 4 mg Revamilast treatment arm and occult blood (fecal occult blood positive) was reported as an AE leading to withdrawal for 1 patient in the placebo treatment arm.
There were no notable mean changes from baseline at any time-point in any treatment arm for any of the vital signs variables.
An abnormal and clinically significant physical examination result was reported in a maximum of 2 patients in any treatment arm at any time-point for any body system.
A number of abnormal and clinically significant ECG results were reported. ECG QT prolonged, reported in 1 patient (0.8%), 2 patients (3.6%), 1 patient (0.8%), and 1 patient (0.9%) in the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms, respectively, and ECG T wave inversion reported in 1 patient (0.8%) in the 4 mg Revamilast treatment arm were reported as TEAEs considered to be related to study medication.

Pharmacokinetic Results: Upon single dose administration ranging from 2 mg to 6 mg, Revamilast (GRC 4039) attained mean C_{max} in the range of 191.208 to 455.715 ng/mL at median T_{max} ranging from 1.259 to 10.500 h at Week 0 (Day 1). Mean values of AUC_{0-t} and $AUC_{0-\tau}$ were reported in the range of 3250.136 to 7625.231 ng.h/mL and 3512.506 to 8569.443 ng.h/mL, respectively, after single dose administration in the range of 2 to 6 mg at Week 0 (Day 1). Revamilast (GRC 4039) upon multiple dose administration with once-daily regimen ranging from 2 to 6 mg attained mean C_{max} of 579.821 to 945.994 ng/mL at median T_{max} ranging from 1.033 to 3.992 h with mean $t_{1/2}$ in the range of 30.987 to 36.715 h at Week 12 (Day 85±2). Mean values of AUC_{0-t}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$ were reported in the range of 34768.760 to 55283.209 ng.h/mL, 11760.873 to 18930.952 ng.h/mL and 24377.284 to 58608.996 ng.h/mL, respectively, at Week 12 (Day 85±2) after multiple doses administered in the range of 2 to 6 mg.
Upon single dose administration of Revamilast ranging from 2 mg to 6 mg, the metabolite GRC 4037 attained mean C_{max} in the range of 14.474 to 30.956 ng/mL at median T_{max} ranging from 11.000 to 24.000 h at Week 0 (Day 1). Mean values of AUC_{0-t} and $AUC_{0-\tau}$ were reported in the range of 223.616 to 375.377 ng.h/mL and 245.388 to 422.131 ng.h/mL, respectively, after single dose administration in the range of 2 to 6 mg at Week 0 (Day 1). GRC 4037 upon multiple dose administration with once-daily regimen ranging from 2 to 6 mg attained mean C_{max} of 34.380 to 50.228 ng/mL at median T_{max} ranging from 3.917 to 11.000 h with mean $t_{1/2}$ in the range of 20.624 to 30.845 h at Week 12 (Day 85±2). Mean values of AUC_{0-t}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$ were reported in the range of 2107.912 to 2708.291 ng.h/mL, 709.397 to

945.473 ng.h/mL and 898.862 to 1541.671 ng.h/mL, respectively, at Week 12 (Day 85±2) after multiple doses administered in the range of 2 to 6 mg.

The exposure of Revamilast (GRC 4039), the parent moiety, appeared to be considerably higher than that of metabolite GRC 4037, with a mean "metabolite to drug $AUC_{0-\tau}$ ratio" of approximately 0.09 and 0.06 upon single and multiple doses respectively across doses ranging from 2 to 6 mg.

Revamilast and its metabolite's mean C_{max} and $AUC_{0-\tau}$ showed a dose-dependent increase at both Week 0 (Day 1) and Week 12 (Day 85±2). Though formal dose proportionality analysis was not performed, it showed a less than proportional increase between 2 to 4 to 6 mg doses.

Pharmacodynamic Results: There was no statistically significant difference in the change from baseline in IL-1, IL-6, or TNF-α values for the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms at Week 12 in the mITT or EE populations. Changes from baseline in CRP and ESR are discussed as part of the secondary efficacy analysis

Conclusions:

- There was no statistically significant difference in the percentage of patients in the 4 mg and 6 mg Revamilast treatment arms achieving an ACR20 response at Week 12 relative to placebo for the mITT or EE populations when the analysis was performed with or without LOCF methodology.
- There were no statistically significant differences relative to placebo in favor of Revamilast 4 mg or 6 mg for any of the secondary efficacy endpoints for the mITT or EE populations when the analysis was performed with or without LOCF methodology.
- There was no statistically significant difference in the percentage of patients in the 2 mg Revamilast treatment arm achieving an ACR20 response at Week 12 relative to placebo for the mITT or EE populations when the analysis was performed with or without LOCF methodology.
- Dosing with 2 mg, 4 mg, or 6 mg Revamilast tablets administered once daily for 12 weeks was generally tolerated well in this study in patients with active RA who have had an inadequate response to MTX.
- Revamilast and its metabolite's mean C_{max} and $AUC_{0-\tau}$ showed a dose-dependent increase at both Week 0 and Week 12. At Week 12, the Revamilast mean C_{max} and $AUC_{0-\tau}$ ranged from approximately 580 to 946 ng/mL and 11761 to 18931 ng.h/mL, respectively.
- The metabolite $AUC_{0-\tau}$ was approximately 6 to 9 % of Revamilast $AUC_{0-\tau}$ upon single and repeat administration of Revamilast at the dose range of 2 to 6 mg.
- There was no statistically significant difference in the change from baseline in IL-1, IL-6, and TNF-α values for the placebo and 2 mg, 4 mg, and 6 mg Revamilast treatment arms at Week 12. There was no notable change in mean CRP or ESR in the placebo or 2 mg, 4 mg, and 6 mg Revamilast treatment arms at Week 12.

Date of Report: 19 Feb 2014