2 SYNOPSIS

Name of Sponsor/ Company: Glenmark Pharmaceuticals SA	Individual Study Table Referring to Part of the Dossier Volume: Page:	(*For National Authority Use only*)
Name of Finished Product: GRC 4039 (INN – Revamilast) tablets of 1, 3 and 5 mg revamilast		
Name of Active Ingredient: Revamilast		

Title of Study: A Phase II, 12-Week Randomised, Double-Blind, Triple Dummy, Parallel Group, Placebo-Controlled, Dose Range Finding Study to Evaluate Safety, Tolerability and Efficacy of Revamilast in Patients With Chronic Persistent Asthma

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The study was conducted at 45 centers in India, Czech Republic, Poland, Russia and United Kingdom.

Publication (reference): None at the time of writing this report.

Study period (years): ~1.5

Date of first subject enrolment: 30-Sep-2011
Date of last subject completed: 08-APR-2013

Phase of development: Phase II

Study Objectives:

Primary Objective:

- To investigate/ evaluate effects of revamilast on lung function in subjects with chronic persistent asthma.

Secondary Objectives:

- To evaluate the safety and tolerability of revamilast in subjects with chronic persistent asthma.
- To investigate the pharmacokinetics (PK) of revamilast and its metabolite GRC 4037 in subjects with chronic persistent asthma.

Methodology:

This was a randomised, double-blind, triple dummy, placebo controlled, parallel group, dose ranging, 12-week study to evaluate the effect of revamilast on lung function in subjects with chronic persistent asthma.

The study was conducted in adult subjects (18 – 65 years of age, inclusive) with a diagnosis of chronic persistent asthma (clinical symptoms and documented reversibility of airway obstruction [≥ 12% and 200 mL increase in FEV_1 following salbutamol]) with an FEV_1 of 50% to 85% (inclusive) of the predicted value. Subjects were recruited after providing informed consent. There were two sub-groups: one on low dose inhaled corticosteroids (ICS) and other non-ICS. Subjects in non-ICS sub-group were either treatment naïve or on preferred step 1 therapy as per GINA 2009. In this sub-group even subjects on alternate step 1 therapy (who entered placebo run-in period and switched to inahaled rapid beta 2 agonist) were included.

In ICS sub-group:

1) Subjects on GINA 2009 step 2 were included.

- If the subjects were on low dose ICS at the time of enrolment were continued in the study, if the dose remained stable in run-in period
- Subjects who were on alternate step 2 therapy per GINA, after proper consent was obtained, were given proper wash-out for their therapies and were switched to low dose ICS

2) Subjects who were on GINA step 3 therapy (either preferred or alternate) were included only if the investigator decided, which was based on clinical judgment and independent of intent to include the subject in the study.

- All the subjects already on alternative step 1 or alternative step 2 therapy and those already on step 3 therapy were required to stop their existing asthma medications and switch to PRN salbutamol (for subjects on alternative step 1 therapy) or low dose ICS plus PRN salbutamol (subjects on alternative step 2 therapy and subjects on step 3 therapy). All subjects requiring such switch of therapy were consented first, as part of the enrolment visit.

- Subjects who were already on as needed inhaled rapid acting beta 2 agonist or low dose ICS + as needed rapid acting beta 2 agonist and who did not require any switch of their medications were also consented during enrolment visit

On the day of enrolment, subjects were consented for participation, and, upon consenting, the investigator prescribed/adviced in writing to "stop" their existing asthma medication and to "switch" to low dose ICS plus PRN salbutamol or only PRN salbutamol, as applicable and provided a date for screening visit spirometry.

The screening visit spirometry was based on:

a) Wash out period for the "prior" asthma medications (i.e., the ones that were stopped upon consenting) and b) Wash out period for the "switched" asthma medications (i.e., the ones subject is "switching to" upon consenting). Since, in most cases the wash out period for (b) was shorter (6 hours for both ICS as well as salbutamol) than the wash out periods for those under (a), the screening visit was scheduled in such a way that there was longest relevant wash out period.

The run-in period for ICS subjects and non-ICS subjects was 4 weeks and 2 weeks respectively, starting from the date of screening visit spirometry. It was to be noted that, once reversibility test was met, it was not repeated. However, if not met, 4 attempts for reversibility over a period of 7 days were allowed as per the protocol. At screening visit 1 (-28 days), ICS subjects who met the inclusion criteria, were followed for 2 weeks for the compliance. At screening visit 2 (-14 days), non-ICS subjects who successfully met the inclusion criteria and ICS subjects who met the compliance to low dose ICS treatment and no asthma exacerbation reported during this period, entered a 2-week single blind placebo run-in period. Subjects who did not experience any episode of asthma exacerbation/worsening were randomised. During the randomisation visit, a subject meeting randomisation criteria was randomly assigned (1:1:1:1) treatment

with one of the three dose regimens of revamilast or placebo (oral tablet, once daily in the morning).

Subjects underwent further 5 visits (at Day 7, Day 28, Day 56, Day 84 and a safety follow-up visit on Day 98). There was a window period of ±2 days for each visit.

During the single blind placebo run-in period subjects received placebo tablets. A compliance check was done at the end of 2 weeks of single blind placebo run-in period to determine the eligibility of the subject for further participation in the study.

During the double blind treatment period on Day 0, subjects received the first dose of study treatment under supervision after completion of visit specific procedures. Then, the subjects were given enough study medication for daily dosing until the next visit. During the entire 12-week double blind treatment period, the subject took four tablets daily from the treatment kit. Adequate instructions about drug dosing were given along with the drug. On all visit days, after the randomisation visit, the investigator took back all the unused study medication from the subject to measure treatment compliance and then dispensed adequate study medication for treatment till next visit except for Visit 3, Visit 7, and Visit 8.

Number of Subjects (planned and analysed):

A total of 240 subjects were planned (60 in each arm) to be randomised. A total of 552 subjects were enrolled of which 550 were screened. A total of 272 subjects were randomised; 271 subjects were included in the safety analysis and 263 included in ITT population for efficacy analysis.

Diagnosis and main criteria for inclusion:

1. Male or female subject aged 18 to 65 years (inclusive).
2. Documented clinical diagnosis of asthma by a physician, based on GINA (2009)
3. Following subjects were included in the study based on GINA (2009) stepwise therapy:
    a. Subject who were currently on preferred or alternative step 1 or step 2 therapy. Subjects on alternate step 1 therapy entered placebo run-in period after appropriate wash out were met and after they switched to inhaled rapid acting beta 2 agonist, upon consenting. Similarly, subjects on alternate step 2 therapy were included after proper washout of therapy and switching to low-dose ICS (plus salbutamol PRN)
    b. Subjects on alternate step 3 therapy and for whom the PI based on clinical judgment and independent of the intent to include subjects in the study were included, but after proper wash out and switching the subjects to low-dose ICS (plus PRN salbutamol)
4. FEV_1 between 50% and 85% (inclusive) of the predicted value for their age, height and gender at screening and shown to be reversible (a ≥12% increase in FEV_1 with an absolute improvement in FEV_1 of at least 200 mL between ≥15 minutes and up to 30 minutes after inhalation of 200 to 400 µg salbutamol via a spacer).
5. Female participants of child bearing potential who had a negative pregnancy test at screening visit. In addition, female of child bearing potential (FCBP) agreed to use TWO of the following contraceptive measures from at least 14 days prior to the first dose of study medication *(i.e., 14 days prior to randomisation)* and continue until 28 days after dosing; combined oral contraceptive, hormonal intrauterine device, non hormonal intrauterine device, bilateral tubal ligation, barrier method of contraception *(condom or occlusive cap [diaphragm/vault caps] with spermicidal foam/gel/film/cream/suppository)*; or vasectomized partner (sole partner). Female not of child-bearing potential *(i.e. are post-menopausal or permanently sterilized [e.g. tubal occlusion, hysterectomy, bilateral salpingectomy])* were not required to use contraception. Female subject of child bearing potential agreed to have serum pregnancy tests during all visits while on study medication and until 2 weeks after taking the last dose of study medication.
6. Males *(including those who had a vasectomy)* agreed to use barrier contraception (latex condoms) when engaging in reproductive sexual activity with FCBP while on study medication and for 90 days after taking the last dose of study medication.

Main criteria of exclusion:

1. Subjects on step 4 or 5 therapy per GINA 2009.
2. Past history of α-1 antitrypsin deficiency.
3. History or suspected hypersensitivity to PDE4 inhibitors.
4. Female subjects on hormone replacement therapy.
5. Change *(within 4 weeks prior to enrolment visit)* in the subject's usual asthma treatment.
6. Past smoker with a history of ≥10 pack-year or current smoker (*i.e. had smoked within the last 12 months prior to screening).*
7. History or suspected hypersensitivity to PDE4 inhibitors.
8. Recent *(within 4 weeks prior to the enrolment visit)* change in the subject's usual asthma treatment.
9. Subjects with risk factors for asthma exacerbation during the study, including *(any of the following):*
    - Current requirement for >8 puffs per day of reliever medication.
    - Hospitalisation for asthma
        i. Within 1 month preceding screening and/or
        ii. More than once in the 6 months preceding screening
    - Treatment with systemic (oral or parenteral) corticosteroid therapy within 1 month of screening or depot corticosteroid therapy within 3 months of screening or receipt of more than 2 short courses of systemic corticosteroid therapy in the preceding year.
10. Evidence of current or recent neoplastic disease *(other than subjects with basal or squamous cell skin cancer who are in remission /stable who are eligible to enter the study).*
11. Any clinically significant cardiovascular, haematological, endocrine, neurological, gastrointestinal, psychiatric, metabolic, immunologic, infectious, hepatic, renal, gynaecological disease or other condition that the investigator considers detrimental to the subject's participation in the study or that might prevent the successful completion of the study:
    a) Any of the following clinically significant laboratory abnormalities:
    - Significant renal insufficiency- Subjects with serum creatinine concentration >1.5 mg/dL.
    - Subjects with a history of proteinuria >300 mg/day
    - Subjects with a clinically significant abnormal WBC count, thrombocytopenia, or anaemia at screening.
    - Subjects with evidence of clinically relevant hepatic disease (e.g. values at screening or at randomisation of more than 1.5 x ULN for aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin or alkaline phosphatase; history of or current bleeding oesophageal varices, ascites, encephalopathy).
    - Positive serology for an infectious disease (including hepatitis B or C) at screening and known case of human immunodeficiency virus [HIV].

    b) Subjects at risk for gastrointestinal haemorrhage (e.g. chronic peptic ulceration).
    c) Subjects with a history of clinically significant cardiovascular disease within the previous 6 months prior to screening *(including, but not limited to, unstable angina, myocardial infarction, stroke, peripheral vascular disease, uncontrolled hypertension, ischemic changes on resting ECG, Congestive cardiac failure of NYHF grade III and IV).*
    d) Subjects who were hospitalised for any psychiatric illness in the past year, or were diagnosed with major depression.
12. Baseline ECG QTc interval >450 ms or any other clinically significant ECG abnormality.
13. Subjects with documented or suspected or current history of alcohol and drug abuse.
14. Subjects who had undergone lung surgery in the previous year.
15. Participation in an investigational drug trial during 30 days (or 9 half lives) preceding screening.

Randomisation criteria:

1. FEV_1 between 50% and 85% (inclusive) of the predicted value for their age, height and gender (before administration of rescue (reliever) medication).

2. Spirometry reproducibility criteria met, i.e., the FEV_1 reading at randomisation was within ± 20% of the value obtained at screening visit. For this purpose, FEV_1 at randomisation were compared to FEV_1 at V2 (for both ICS and non-ICS subjects). In case reversibility testing was applicable (i.e., for non-ICS subjects, for whom V2 was the only screening visit), the comparison for 'reproducibility' considered FEV_1 before administration of salbutamol for reversibility testing for V2.
3. Any symptom score (and not necessarily the same symptom score on each day) being ≥1 for at least 4 out of the last 7 days of the run-in (based on the subject diary, with the day before the randomisation visit being Day 7).
4. Use of salbutamol for symptom relief on >2 occasions *(defined as ≥1 puff administered during the day AND ≥1 puff administered during the night OR a total of ≥2 puffs daily [24 hours]),* on at least 4 out of the last 7 days of the run-in *(based on the patient diary, with the day before the randomisation visit being Day 7)*.
5. No asthma exacerbation during the run-in period.
6. Ability to perform adequate spirometry test, defined as having a minimum of 3 acceptable manoeuvres, and having met spirometry repeatability criteria as per ATS/ERS guidelines *(i.e. the difference between the largest and second largest FEV_1 is ≤0.150L).*
7. ECG and clinical laboratory determinations from screening for ICS arm (Visit 1) and screening for non-ICS arm (Visit 2) must be within normal ranges, unless abnormalities were deemed by the Investigator as clinically non-significant.
8. For ICS-subjects: No change in ICS i.e. the corticosteroid used, dose and frequency in last 4 weeks.
9. The subject demonstrated compliance with:
    a. Withholding of disallowed concomitant medications,
    b. Single-blind study drug dosing instructions- ≥80% compliance

Test product, dose and mode of administration, Lot number:

Revamilast tablets (strength 1 mg, 3 mg, and 5 mg) and the matching placebo tablets for oral administration were manufactured on behalf of sponsor by Glenmark Generics Ltd, India as per the applicable regulations. The 3 different dose regimens of the active drug that were used in the study during the treatment period were revamilast 2 mg OD, revamilast 4 mg OD, and revamilast 6 mg OD administered orally.

Study Drug	Lot Number/s
GRC 4039 tablets 1 mg	02103422
GRC 4039 tablets 3 mg	02103421, 02111280
GRC 4039 tablets 5 mg	02103423, 02111281

Duration of treatment: 12 weeks

Reference therapy, dose and mode of administration, batch number:

The placebo tablets matching to Revamilast 1 mg, 3 mg and 5 mg were used in the study.

Matching placebo tablets were administered orally.

Study Drug	Lot Number/s
Placebo for GRC 4039 tablets 1 mg	02103303, 02111268
Placebo for GRC 4039 tablets 3 mg	02103304, 02111274
Placebo for GRC 4039 tablets 5 mg	02103305, 02111275

Criteria for evaluation:

Efficacy: Efficacy was evaluated based on the following variables

- FEV_1, PEF, FVC, forced expiratory flow 25-75% ($FEF_{25-75\%}$) as measured by Spirometry.
- Daily PEF monitoring: Morning and evening PEF were assessed using the provided peak flow meter

- Asthma symptoms reported by subjects in their diary
- Reliever medication used by the subject
- Asthma exacerbations
- Investigator's global impression of change and Patient's global impression of change

Safety: Safety was assessed based on physical examination, vital signs, ECG, clinical laboratory, safety tests, and adverse events.

Pharmacokinetics: Pharmacokinetic assessments of revamilast (GRC 4039) and its metabolite GRC 4037 were carried out using WinNonlin Professional Software (Version 5.3 or higher) from the plasma concentration data from Visit 3 and Visit 7 samples.

Statistical methods:

Analysed Populations

- All Randomised Population: All subjects who met the randomisation criteria and were randomised to double-blind study treatment were included in the all randomised population.
- Safety population: All subjects who
  - were randomised and
  - had received at least one dose of double-blind study treatment.

Subjects who received study treatment other than that intended were analysed according to the study treatment received.

- ITT population: All subjects who:
  - were randomised to double-blind study treatment,
  - had received at least one dose of study treatment, and
  - had primary efficacy data (morning pre-dose FEV_1) at both baseline and at least one post-baseline visit.

Subjects were analysed according to the study treatment they were randomised to.

- PP population: All subjects who
  - were included in ITT population, and
  - without any major protocol deviations that would affect primary efficacy endpoint evaluation.
- Pharmacokinetic population: All subjects who
  - were included in safety population,
  - signed the pharmacokinetic consent, and
  - had at least one post-baseline pharmacokinetic plasma sample (rich or sparse) taken and analysed.

Descriptive statistics (number of observations (n), arithmetic mean (Mean), Least square mean (LSM), Standard Error (SE), standard deviation (SD), median, minimum and maximum (Min - Max) were presented in the summary tables for continuous data. "n" was presented with no decimal place, Mean and Median were presented up to one more decimal place from the original value, SD two decimal places from the original value and Min – Max as an original value. For categorical data, frequency counts (n) and percentage (%) were presented. The frequencies were presented up to 0 decimal places and percentages up to 1 decimal place.

All inferential analysis was carried out at level of significance (α) = 0.05 unless otherwise specified. All recorded and derived data were listed for each subject.

A close test approach was adopted to overcome multiplicity while performing the primary analysis for efficacy using ITT population. The ANCOVA model using CONTRAST statement in SAS was used for pair-wise comparison. In the first instance highest dose was compared with placebo, only if null hypothesis was rejected, second highest dose was then compared with placebo and not otherwise. This process was continued until all treatment doses were compared or until the null hypothesis was accepted.

All secondary efficacy parameters were summarised by treatment. ANCOVA models similar to the primary efficacy analysis model were performed on secondary efficacy parameters, as appropriate, including morning PEF data from diaries.

Secondary endpoints of interest included:

- Change from baseline at Days 7, 28, and 56 for morning pre-dose FEV_1.
- Change from baseline at Days 7, 28, 56 and 84 in morning pre-dose FVC, PEF, $FEF_{25-75\%}$.
- Area under the curve (AUC) of change from baseline morning pre-dose FEV_1 measured at each visit to Day 84.
- Change from baseline in morning and evening PEF on Days 7, 28, 56 and 84 (based on subject diary).
- Change from baseline at Days 7, 28, 56 and 84 in morning pre-dose FEV_1, FVC, PEF, $FEF_{25-75\%}$, PEF for ICS and non-ICS sub-group.
- Change in asthma day time symptom score from baseline at Day 84.
- Change in asthma night time symptom score from baseline at Day 84.
- Change in number of night time awakenings from baseline at Day 84.
- Frequency and the use of rescue (reliever) medication (salbutamol).
- Frequency and severity of asthma exacerbations.
- Investigator global impression of change from baseline to Day 84.
- Patient global impression of change from baseline to Day 84.
- Plasma pharmacokinetics of revamilast and its metabolite GRC 4037.
- Change from baseline in blood cell counts to Day 84.

Pharmacokinetics analyses:

Pharmacokinetic assessments of revamilast (GRC 4039) and its metabolite GRC 4037 were carried out using WinNonlin Professional Software (Version 5.3 or higher) from the plasma concentration data from Visit 3 and Visit 7 samples.

Derived PK parameters (AUCs, maximum plasma concentration [C_{max}], time after dosing at which C_{max} occurs [t_{max}] and terminal half-life [$t_{1/2}$]) were estimated using appropriate validated software. Subjects profile and within- treatment groups graphs were produced for each parameter as appropriate. Pharmacokinetic analysis and results are summarised here and presented within a separate analysis plan and report.

Safety Analyses

All safety summaries are presented using the safety population. The adverse events (AEs) reported in during the run-in period were presented separately. All AEs were coded by SOC and PT using MedDRA version 15.0.

The safety analysis was performed on following safety parameters:

- Adverse event
- Physical examinations
- Vital signs (blood pressure, heart rate, respiratory rate, temperature and body weight)
- Electrocardiogram
- Clinical laboratory test (hematology, coagulation, biochemistry, serology and urinalysis)

Summary

Disposition, Demographics and Baseline Characteristics

Disposition and Analysis Sets

A total of 552 subjects were enrolled across 45 centers in India, Czech Republic, Poland, Russia and United Kingdom. Of the 552 subjects enrolled, 550 (*includes 1 subject – 81020, who was screened and completed the study, however the eligibility confirmation record is missing, hence not considered as randomised and was not included in the analysis)* were screened and 279 *(includes 2 subjects – 49002 and 49003, for whom the screening visit is missing but are screen failure on EOS as per CRF)* were screen failures. A total of 272 subjects were randomised, of which 263 subjects were included in ITT population and 271 in safety population *(Subject no. 76004 was randomized but not dosed so not calculated in the safety population).* A total of 223 (82%) subjects completed the study. The number of subjects completing the treatment period was almost similar across the treatment groups.

A total of 49 (18%) subjects discontinued from the study. The most common reason for discontinuation was lost to follow-up (12 [4.4%]), followed by failure to comply with the study procedures (10 [3.7%]), positive faecal occult blood (9 [3.3%]), safety reasons as Judged by the Investigator and/or Glenmark Pharmaceuticals SA (8 [2.9%]), subject withdrew consent (6 [2.2%]), diarrhea with ≥3 episodes (2 [0.7%]), and pregnancy and SAE (1 [0.4%], each).

Demographics

Overall mean age of subjects in ITT population was 41.6 ±11.81 years.The mean body mass index (BMI) was slightly higher in the REVA 2 mg group as compared to other three treatment groups. The majority of subjects across the treatment groups were Asian (82.1% to 89.1%). Overall, the number of females was higher (59.3%) than the males (40.7%).. The median duration of asthma across the treatment groups ranged between 7.2 years to 9.4 years.

The subjects who met the spirometry washout criteria were almost similar across all the treatment groups. A total of 244 (92.8%) subjects met spirometry washout criteria and out of which 19 (7.2%) required repeat spirometry to meet the washout criteria.

Baseline Characteristics

The mean percentage predicted pre-bronchodilator FEV_1 was from 63.1% to 65.5% among the treatment groups and the mean percentage predicted post-bronchodilator FEV_1 was from 77.5% to 81.1% among the groups. All the subjects met reversibility.

The percentage of subjects with at least one medical and surgical history history in safety population ranged from 52.2% to 68.7% among the treatment groups. Symptoms or incidence of asthma were not recorded in the respiratory, thoracic and mediastinal disorders SOC as they pertained to the disease being studied. The most commonly reported medical history was in the SOC of surgical and medical procedures, followed by respiratory, thoracic and mediastinal disorders, infections and infestations, vascular disorders, and immune disorders.

Efficacy Results

Primary Efficacy Results:

The results of primary analysis of the change in the pre-dose FEV_1 from Day 0 to Day 84 showed that the improvements in mean FEV_1 in all the 3 revamilast-treated groups were numerically higher than that in placebo-treated group. However, none of the revamilast groups showed statistically significant higher improvements over placebo. Mean values of the improvements in FEV_1 at Day 84 were 0.042, 0.084, 0.070 and 0.011 L for 2 mg, 4 mg & 6 mg revamilast and placebo groups, respectively. Similar findings were also observed for the primary endpoint in ICS and non-ICS subgroups.

Comparision of Among Treatment Groups with Respect to Change in Morning Pre-Dose FEV1 (L) From Day 0 to Day 84 – ITT Population

Visit	Statistics	REVA2 (N=64)	REVA4 (N=68)	REVA6 (N=67)	Placebo (N=64)	Total (N=263)
Visit 3 (Day 0)	N	64	68	67	64	263
	Mean (SD)	1.790 (0.5211)	1.828 (0.5217)	1.947 (0.5020)	1.921 (0.5603)	1.872 (0.5273)
	Median	1.770	1.820	1.920	1.850	1.850
	Min – Max	0.80 - 3.04	0.79 - 2.89	0.95 - 3.44	1.04 - 3.13	0.79 - 3.44
Visit 7 (Day 84)	N	55	60	61	60	236
	Mean (SD)	1.766 (0.6301)	1.909 (0.6309)	2.009 (0.5589)	1.905 (0.5755)	1.901 (0.6012)
	Median	1.680	1.800	1.990	1.760	1.845
	Min – Max	0.78 - 4.39	0.81 - 3.41	0.93 - 3.12	1.03 - 3.17	0.78 - 4.39
Change from Visit 3 to Visit 7	N	55	60	61	60	236
	Mean (SD)	0.042 (0.2953)	0.084 (0.2303)	0.070 (0.3427)	0.011 (0.2893)	0.052 (0.2918)
	Median	0.020	0.035	0.020	-0.015	0.030
	Min – Max	-0.77 - 1.52	-0.52 - 0.67	-1.25 - 1.08	-0.87 - 0.73	-1.25 - 1.52
	P value vs placebo	0.6405	0.4566	0.6357		

Seconday Efficacy Results:

The results of secondary endpoints of change from baseline at Days 7, 28, and 56 for morning pre-dose FEV_1, change from baseline at Days 7, 28, 56 and 84 in morning pre-dose FVC, PEF, $FEF_{25-75\%}$, AUC of change from baseline morning pre-dose FEV_1 measured at each visit to Day 84, change from baseline in morning and evening PEF on Days 7, 28, 56 and 84 (based on patient diary), change from baseline to Days 7, 28, 56 and 84 in morning pre-dose FEV_1, FVC, PEF, FEF25-75%, PEF for ICS and non-ICS subgroups, change in asthma day time symptom score from baseline to Day 84, change in asthma night time symptom score from baseline to Day 84 were also similar across all the treatment groups. The LSM change for AUC from baseline morning pre-dose FEV_1 to Day 84, change in number of night time awakenings from baseline to Day 84, Investigator global impression of change from baseline to Day 84, and Patient global impression of change from baseline to Day 84 were almost similar across all the treatment groups. The percentage of days salbutamol was used was similar in all the treatment groups. There were some changes seen in frequency and severity of asthma exacerbations. In ICS subgroup, decrease in FEV_1 of ≥20% compared to baseline, nocturnal awakening due to asthma requiring salbutamol on any ≥2 nights during 7 consecutive days and use of ≥8 puffs/day of salbutamol on any ≥3 days during 7 consecutive days was higher in the placebo group as compared to three treatment groups. In non-ICS subgroup, decrease in FEV_1 of ≥20% compared to baseline and decrease in morning PEF to ≥20% compared to baseline and use of ≥8 puffs/day of salbutamol on any ≥3 days during 7 consecutive days was more in the placebo group as compared to all the three treatment groups. There were changes, noted in the blood cell counts (total Leucocytes (WBC) count, neutrophil count, lymphocyte count, monocyte count, eosinophil count,basophil count, erythrocyte count, haemoglobin, MCH, MCHC, PCV and platelet count) from baseline to Day 84 REVA 2 mg, REVA 4 mg, REVA 6 mg and placebo groups, which were not clinically significant..

Upon single dose administration ranging from 2 mg to 6 mg at Visit 3 (Day 0), revamilast (GRC 4039) attained mean C_{max} in the range of 177.183-434.599 ng/mL at median T_{max} ranging from 9.000-11.000 h, mean values of AUC0-t and AUC0-τ were reported in the range of 3211.251-7138.252 ng.h/mL and 4160.714-7852.077 ng.h/mL, respectively. Revamilast (GRC 4039) upon multiple dose administration with once daily regimen ranging from 2-6 mg at Visit 7 (Day 84), attained mean C_{max} of 449.548-1051.520 ng/mL at median T_{max} ranging from 1.000-4.000 h with mean $t_{1/2}$ in the range of 28.046-36.293 h. Mean values of AUC_{0-t}, $AUC_{0\,\tau}$ and $AUC_{0-\infty}$ were reported in the range of 19219.948-44654.891 ng.h/mL, 9056.903-19389.494 ng.h/mL, and 19128.031-52330.653 ng.h/mL, respectively at Visit 7.

Upon single dose administration of revamilast ranging from 2 mg to 6 mg at Visit 3 (Day 0), the metabolite GRC 4037 attained mean C_{max} in the range of 3.739-12.060 ng/mL at median T_{max} ranging from 17.459-24.000 h. Mean values of AUC_{0-t} and $AUC_{0-\tau}$ were reported in the range of 57.053-

184.428 ng.h/mL and 97.115-276.300 ng.h/mL, respectively at Visit 3. GRC 4037 upon multiple dose administration of GRC 4039 with once daily regimen ranging from 2-6 mg at Visit 7 (Day 84), attained mean C_{max} of 15.852-49.974 ng/mL at median T_{max} ranging from 0.000-11.000 h. Mean values of AUC_{0-t} and $AUC_{0-\tau}$ were reported in the range of 740.691-2422.281 ng.h/mL and 307.947-892.732 ng.h/mL, respectively at Visit 7. The exposure of revamilast (GRC 4039), the parent moiety appeared to have considerably higher than that of metabolite GRC 4037 and the resultant mean "metabolite to drug $AUC_{0-\tau}$ ratio" were reported in the range of 0.017-0.050 and 0.035-0.063 upon single and multiple doses respectively across doses ranging from 2-6 mg..

Overall, at the doses evaluated in this study, there were improvemnts in FEV_1 in subjects with chronic persistent asthma treated with revamilast. The improvements in 6 mg and 4 mg treatment groups were relatively better than those in 2 mg and placebo groups. On top of this, the difference in FEV_1 from baseline was more clear and uniform over time in the ICS subgroup than that in the non-ICS subgroup. However, the difference over placebo did not achieve statistical significance in any of the revamilast groups.

Safety Results:

Most patients had (>40%) adverse events of mild intensity. The most common adverse events (>5%) seen in the study were faecal occult blood positive, diarrhoea, pyrexia and asthma. Apart from expected PDE4 class effects such as diarrhoea, nausea, and vomiting, there were no serious events due to the study drug. There were no deaths in the study. There were 5 (1.3%) treatment-emergent SAEs reported in 3 subjects in the study none of which was related to the study drug. Hence, GRC 4039 in adult subjects with chronic persistent asthma is expected to be safe and well tolerable up to a dose of 6 mg daily for 12 weeks.

Conclusion:

In this study, revamilast as compared to placebo showed relatively higher improvement in morning FEV_1 at Day 84 (Week 12) over Day 0 (Week 0). However, the improvement (mean value) was less than 100 mL and did not reach statistical significance. Safety data showed that revamilast is tolerable and safe for use in adult subjects with chronic persistent asthma up to a dose of 6 mg for 3 months.

Further studies might be required to investigate the usefuleness of GRC 4039 in chronic asthma subjects.