2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
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Name of Active Ingredient: CC-10004		

Title of Study:

A phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, to compare the efficacy and safety of two doses of apremilast (CC-10004) in subjects with active rheumatoid arthritis who have had an inadequate response to methotrexate

Principal Investigator:

Investigators:

Study center(s): 42 centers in the Czech Republic, Poland, and the United States.

Publications (reference): None.

Studied period (years):		**Phase of development:** 2
Date first subject enrolled:	27 Dec 2010	
Date last patient last visit:	27 Aug 2012	

Objectives:

The primary objective of the study was to evaluate the efficacy of 2 doses of apremilast (20 mg twice daily [BID] and 30 mg BID), compared with placebo, on the reduction of signs and symptoms of rheumatoid arthritis (RA) at 16 weeks of treatment.

The secondary objectives of the study were:

- To evaluate the following in subjects with active RA who were treated with 2 doses of apremilast compared with placebo for up to 24 weeks:
  - Safety and tolerability
  - Physical function

  (The measures of signs and symptoms assessed at Week 16 were also evaluated at Week 24.)
- To evaluate the following in subjects with active RA who were treated with 2 doses of apremilast for up to 52 weeks:
  - Safety and tolerability
  - Signs and symptoms
  - Physical function
- To evaluate the efficacy, safety and tolerability of 2 doses of apremilast for up to 2 years of administration in subjects with active RA

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The structure objectives of the study were:

- To evaluate the efficacy of 2 doses of apremilast, compared with placebo, for inhibition of structural damage assessed by magnetic resonance imaging (MRI) after 16 weeks of treatment in a subset of subjects
- To evaluate the efficacy of 2 doses of apremilast, compared with placebo, for inhibition of structural damage assessed by radiography for up to 52 weeks of treatment
- To evaluate the long-term efficacy of apremilast for inhibition of structural damage as assessed by radiography for up to 2 years of treatment

The health-related quality-of-life objectives of the study were:

- To evaluate the efficacy of 2 doses of apremilast, compared with placebo, on the health-related quality-of-life evaluations for up to 24 weeks of treatment
- To evaluate the efficacy of 2 doses of apremilast on the health-related quality-of-life evaluations for up to 2 years of treatment

The exploratory objectives of the study were:

- To evaluate the effect of 2 doses of apremilast compared with placebo on the time to response
- To evaluate the number of subjects in each treatment group who achieved 0 swollen and tender joints for up to 2 years

The pharmacokinetic/pharmacodynamic objectives of the study were:

- To characterize the pharmacokinetics (PK) of 2 doses of apremilast in a subset of subjects with active RA
- To explore the pharmacodynamics (PD)/biomarkers effects of 2 doses of apremilast in a subset of subjects for up to 36 weeks

The pharmacogenetic (PG) objective of the study was to compare PG markers associated with clinical response to 2 doses of apremilast with placebo in subjects with active RA.

Methodology: This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study design with 2 active treatment groups on top of stable background methotrexate (MTX) therapy in subjects with active RA who had an inadequate response to MTX.

Patients were randomized 1:1:1 (70 per dose group) to receive either apremilast 20 mg BID (APR 20 BID), apremilast 30 mg BID (APR 30 BID), or identically appearing placebo for 24 weeks.

At Week 16, all subjects whose swollen and tender joint scores had not improved by ≥ 20% entered early escape and received blinded active treatment. Subjects in the placebo group transitioned in a blinded fashion to receive APR 20 BID. Subjects on active treatment who met the early escape criteria continued, in a blinded fashion, to receive the same dosage to which they were originally assigned.

At Week 24, all remaining subjects in the placebo group were to be transitioned to APR 20 BID in a

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blinded fashion. Subjects on blinded apremilast were to remain at the same dose levels, remaining blinded to dose.

At Week 52, subjects were to have the option to enter a double-blind, active treatment extension phase for 1 additional year. Subjects were to continue on their assigned treatment from Week 52 through the 1-year extension phase, for a total study treatment time of 2 years. Upon determination of the final optimal dose of apremilast (20 mg BID or 30 mg BID), all subjects were to be transitioned to the selected dose.

Clinical efficacy for amelioration of signs and symptoms of RA (ie, American College of Rheumatology [ACR] 20, ACR 50, and ACR 70) and physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]) were to be assessed at Weeks 16, 24, and 52, and at Year 2. Radiography for the evaluation of joint damage was to be completed on all subjects at Weeks 0, 24, and 52, and at Year 2. Additionally, an MRI evaluation for the inhibition of structural damage was to be completed at Weeks 0 and 16 in a subset of approximately 30 subjects per treatment group.

Number of subjects (planned and analyzed):

Planned: 210 subjects

Analyzed: 237 subjects

Diagnosis and main criteria for inclusion:

For inclusion into the trial, subjects were required to fulfill all of the following criteria:

1. Male or female, age ≥ 18 years at the time of consent.
2. Understood and voluntarily signed an informed consent form prior to any study related assessments/procedures.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Had a documented diagnosis of RA (1987 ACR Criteria) with onset of signs/symptoms of disease ≥ 4 months of duration from randomization.
5. Were receiving treatment on an outpatient basis.
6. Had active disease despite current MTX treatment as defined below:
   - ≥ 6 swollen joints (66 swollen joint count) at randomization (Visit 2) **AND**
   - ≥ 6 tender joints (68 tender joint count) at randomization (Visit 2)
7. Met at least 1 of the 4 lab requirements below:
   - High-sensitivity C-reactive protein (hs-CRP) ≥ 10 mg/L
   - Erythrocyte sedimentation rate (ESR) > 28 mm after the first 1 hour
   - Positive for rheumatoid factor

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- Positive for anti-cyclic citrullinated peptide antibodies

8. For subjects participating in the MRI assessment:
   - Had RA joint involvement, as assessed by swollen joint counts in: 1) at least 2 metacarpophalangeal (MCP) swollen joints on the same hand, or 2) at least 1 swollen MCP joint and swollen wrist on the same hand.
9. Treated with MTX for at least 4 months prior to randomization, and must have been on a stable dose between 7.5 and 25 mg/week (oral or parenteral) for at least 4 weeks prior to randomization. Subjects were required to maintain their stable dose through Week 52 of the study. Oral folate (folic acid) supplementation was required with a minimum dose of 5 mg/week, or instead leucovorin may have been used up to 10 mg/week orally.
10. Non-steroidal anti-inflammatory drugs and pain medications were allowed; however, the subject must have been on a stable regimen for at least 7 days prior to randomization and through Week 52 of the study.
11. Oral corticosteroids (if taken) were allowed; however, subjects must have been on a stable dose of prednisone ≤ 10 mg/day or the equivalent for at least 28 days prior to randomization and through Week 52 of the study.
12. Met the following laboratory criteria at screening:
    - White blood cell count ≥ 3,000/mm^3 (≥ 3.0 x 10^9/L) and < 14,000/mm^3 (< 14 x 10^9/L)
    - Platelet count ≥ 100,000/μL (≥ 100 x 10^9/L)
    - Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)
    - Aspartate transaminase (serum glutamic oxaloacetic transaminase) (AST [SGOT]) and alanine transaminase (serum glutamate pyruvic transaminase) (ALT [SGPT]) ≤ 2 x upper limit of normal (ULN). If initial test showed ALT or AST > 2 times the ULN, 1 repeat test was allowed during the screening period.
    - Total bilirubin ≤ 2 mg/dL (≤ 34 μmol/L). If initial test result was > 2 mg/dL, 1 repeat test was allowed during the screening period.
    - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)
    - Hemoglobin A1c ≤ 9.0%
    - Negative for hepatitis B surface antigen
    - Negative for hepatitis C antibody
13. Male subjects (including those who have had a vasectomy) who engaged in activity in which conception was possible were required to use barrier contraception (male latex condom or

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nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on the investigational product (IP) and for at least 28 days after the last dose of IP.

14. Females of child bearing potential (FCBP) were required to have a negative pregnancy test at screening and baseline. Any FCBP who engaged in activity in which conception was possible must have used contraception (effective by the time the subject was randomized into the study) while on IP and for at least 28 days after taking the last dose of IP, with either: 1) one highly effective form (non-oral hormonal, intrauterine device, tubal ligation, vasectomized partner); or 2) an oral hormonal contraceptive PLUS 1 additional form of barrier contraception (male or female latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane], diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide); or 3) two forms of barrier contraception (male or female latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) PLUS 1 of the following (diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide).

Any of the following was regarded as a criterion for exclusion from the trial:

1. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization.
2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis or significant systemic involvement secondary to RA (eg, vasculitis, pulmonary fibrosis or Felty syndrome). Sjögren syndrome secondary to RA was allowable.
3. Functional Class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis.
4. Prior history of, or current, inflammatory joint disease other than RA (eg, gout, reactive arthritis, psoriatic arthritis, ankylosing spondylitis, Lyme disease).
5. Receiving treatment with disease-modifying antirheumatic drugs (DMARDs) (other than MTX), including biologic DMARDs. Previous use was only allowed after adequate washout prior to randomization.
6. Inadequate response to treatment with an anti-tumor necrosis factor (TNF) agent. Subjects who terminated previous anti-TNF treatment due to cost or safety reason, such as discomfort with the subcutaneous injections, were permitted to participate in this study after adequate washout.
7. Treatment with any investigational agent within four weeks (or 5 half-lives of the investigational drug, whichever was longer) of screening.
8. Previous treatment with any cell-depleting therapies, including investigational agents (eg,

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CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19 and anti-CD20).

9. Treatment with intravenous gamma globulin, plasmapheresis or Prosorba® column within 6 months of baseline.
10. Intra-articular or parenteral corticosteroids were not allowed within 6 weeks prior to randomization.
11. Any previous treatment with alkylating agents such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.
12. Pregnant women or nursing (breast feeding) mothers.
13. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including severe or very severe chronic obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus as defined by hemoglobin A1c (HbA1c) > 9.0%) or gastrointestinal disease.
14. Uncontrolled disease states, such as asthma, psoriasis or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids.
15. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, Hepatitis B and C, and herpes zoster, but excluding onychomycosis) or any major episode of infection requiring hospitalization or treatment with intravenous or oral antibiotics within 4 weeks of screening.
16. History of positive Human Immunodeficiency Virus test or congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency Disease).
17. History of malignancy, including solid tumors and hematologic malignancies (except basal cell carcinoma of the skin that has been excised and cured).
18. History of alcohol, drug or chemical abuse within the 6 months prior to screening.
19. Any significant medical condition, laboratory abnormality, or psychiatric illness that would have prevented the subject from participating in the study.
20. Any condition including the presence of laboratory abnormalities that would have placed the subject at unacceptable risk if he/she were to participate in the study.
21. Any condition that in the investigator's opinion would have interfered significantly with the efficacy evaluations, including the pain and joint assessments (eg, fibromyalgia).

Additionally, the following were considered criteria for exclusion from the MRI substudy:

22. Receiving medication(s) or was expected to require medication(s) during the study that impacted vascular flow (eg, nitrates, calcium channel blockers, ergot containing drugs) on the day of the MRI test and in the investigator's judgment the subject was not able to hold back from taking

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these medications on the day of the MRI prior to the MRI test. The subject could have continued taking the medication(s) at any time after the MRI test was completed, as clinically indicated and scheduled. Exclusions of antihypertensive and migraine medications were determined after discussion with the Sponsor.

23. Unable to undergo an MRI examination, including but not limited to the presence of a pacemaker, defibrillator, or other implanted device such as anterior interbody cages, aneurysm clip, pedicle screws, or any other metal contained in the body (eg, such as tattoos that contain metallic pigment, or metal in the eyes from metal grinding [eg, a metal worker, etc.]), or severe claustrophobia, or any other contraindication to an MRI as per local imaging center guidelines.
24. Allergic or adverse reactions to gadolinium.
25. Estimated glomerular filtration rate below 60 mL/min/1.73 m^2 (based on the Modification of Diet in Renal Disease formula).

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

Apremilast administered as 10-, 20-, or 30-mg tablets.

Batch numbers:

Apremilast 10-mg tablets: 10B0036, 10B0353

Apremilast 20-mg tablets: 10B0037, 10B0038, 10B0355, 10B0201, 10B0202, 11B0100, 11B0109

Apremilast 30-mg tablets: 10B0040, 10B0041, 10B0239, 10B0211, 11B0104, 11B0163

Duration of treatment:

Subjects were to be treated with APR 20 BID, APR 30 BID or placebo for 24 weeks, followed by an active treatment period in which all subjects were to be treated with APR 20 BID or APR 30 BID for up to 2 years in total.

At Week 16, all subjects whose swollen and tender joint scores had not improved by ≥ 20% entered early escape and received blinded active treatment. Subjects in the placebo group transitioned in a blinded fashion to receive APR 20 BID. Subjects on active treatment who met the early escape criteria continued, in a blinded fashion, to receive the same dosage to which they were originally assigned.

The Data Monitoring Committee (DMC) met on 24 May 2012 to review data through Week 24. They recommended stopping the study due to an apparent lack of clinical efficacy (failing to achieve the primary endpoint [American College of Rheumatology (ACR) 20 at Week 16]) at the doses explored in this study in subjects with RA receiving concomitant MTX. Celgene reviewed the data, agreed with the recommendation of the DMC, and the study was halted, effective 05 July 2012. This is the final study report for Study CC-10004-RA-002, and presents data through study termination.

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

Placebo administered as tablets.

Lot numbers:

Placebo 10-mg tablets: 10B0005, 10B0207, 10B0348, 11B0170, 11B0220

Placebo 20-mg tablets: 10B0006, 10B0052, 10B0053, 10B0044, 10B0059, 10B0241, 10B0270, 10B0350, 11B0110, 11B0111, 11B0165

Placebo 30-mg tablets: 10B0010, 10B0045, 10B0054, 10B0209, 10B0351, 10B0056, 10B0062, 10B0081, 10B0240, 10B0352, 10B0363, 11B0152

Criteria for evaluation:

Efficacy: Efficacy was primarily assessed as the ACR 20 response at Week 16, which was defined as a ≥ 20% improvement from baseline in the tender and swollen joint counts plus ≥ 20% improvement from baseline in 3 of the following 5 assessments: subject's and physician's global assessment of disease activity, HAQ-DI score, subject assessment of pain, and the acute phase reactant (CRP or ESR).

In addition to the time points listed, secondary endpoints were to have been evaluated at Year 2. Due to early termination of the study, the Year 2 assessments were not performed. The secondary efficacy endpoints were:

- Change from baseline in physical function using the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16, Week 24, and Week 52
- Proportion of subjects who achieved ACR 20 at Week 16, Week 24, and Week 52
- Proportion of subjects who achieved ACR 50 at Week 16, Week 24, and Week 52
- Proportion of subjects who achieved ACR 70 at Week 16, Week 24, and Week 52
- Change from baseline in Short Form 36-Item Health Survey (SF-36) Physical Function domain score at Week 16, Week 24, and Week 52
- Change from baseline in Clinical Disease Activity Index (CDAI) at Week 16, Week 24, and Week 52
- Proportion of subjects who achieved low disease activity or remission based on the CDAI ≤ 10 at Week 16, Week 24, and Week 52
- Change from baseline in Disease Activity Score (DAS28) at Week 16, Week 24, and Week 52
- Percentage change from baseline in the individual ACR components at Week 16, Week 24, and Week 52
- Change from baseline in Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-Fatigue) score at Week 16, Week 24, and Week 52
- Proportion of subjects who achieved an improvement of ≥ 0.22 units from baseline in the HAQ-DI at Week 16, Week 24, and Week 52
- Proportion of subjects who achieved an improvement of at least 4 units from baseline in the FACIT-Fatigue at Week 16, Week 24, and Week 52

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- Proportion of subjects who achieved European League Against Rheumatism (EULAR) response criteria at Week 16, Week 24, and Week 52

The structure endpoints were:

- Change from baseline in total rheumatoid arthritis magnetic resonance imaging scoring (RAMRIS) score, RAMRIS components and joint space narrowing in the subset of subjects in each treatment group at Week 16
- Change from baseline in van der Heijde Modified Total Sharp Score (vdH-TSS) of the radiography and its components in each treatment group at Week 24 and Week 52

The exploratory endpoints were:

- Time to ACR 20, ACR 50, and ACR 70 response in the first 16 weeks of treatment
- Proportion of subjects in each treatment group who achieved: 1) zero swollen joints, or 2) zero tender joints, or 3) both zero swollen and zero tender joints

The pharmacokinetic and pharmacodynamic endpoints were:

- To characterize the systemic exposure of apremilast (20 mg BID and 30 mg BID) based on the intensive PK at Week 12 (ie, blood draws at predose and up to 8 hours postdose):
  - Area under the plasma concentration – time curve
  - Peak (maximum) plasma concentration of apremilast
  - Time to maximum plasma concentration of apremilast
- To characterize the systemic exposure of apremilast (20 mg BID and 30 mg BID) based on the population (sparse) PK parameters, drug clearance and volume of distribution determined from samples collected at Weeks 4, 16, and 24
- To evaluate the change from baseline in plasma pro-inflammatory protein levels at Weeks 4, 16, and 24 in a subset of subjects in each treatment group with active RA

The pharmacogenetic (PG) endpoint of this study was to compare the PG markers associated with a clinical response to apremilast (APR 20 BID and APR 30 BID) versus placebo as defined by the ACR 20 at Week 16 in subjects with active RA.

Safety: Safety was measured with adverse events (AEs); chest radiographs; vital signs, including height and weight; physical examination; clinical laboratory variables; pregnancy test; 12-lead electrocardiogram (ECG); and estimated glomerular filtration rate. The estimated glomerular filtration rate was evaluated for subjects participating in the MRI assessment to confirm adequate kidney function prior to administration of gadolinium.

Statistical methods:

For table presentation, categorical data (number of subjects who achieved an ACR 50, ACR 70, EULAR response, DAS28 remission [DAS28 < 2.6], CDAI response [CDAI ≤ 10] FACIT-fatigue response [FACIT-fatigue improvement ≥ 4], or at least a 0.22-unit improvement in HAQ-DI) were summarized using frequency counts. The chi-Square test was used to compare the active treatment groups to placebo. For Week 24 analyses, subjects who met the early escape criteria were counted as non-responders. For continuous endpoints (HAQ-DI, FACIT-Fatigue, SF-36v2 domain scores, CDAI, and DAS28), summary

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statistics at each time point were provided for the baseline, time point, and change (and percent change) from baseline values among subjects who had both values at baseline and at the time point. For Week 24 analyses, the Week 16 evaluation was used for all subjects who met the early escape criteria at Week 16. An analysis of covariance (ANCOVA), with treatment as the factor in the model and the baseline scores as the covariate, was used to compare the treatment groups.

Demographics:

Subjects' age, weight, height, and other continuous demographic and baseline characteristics were summarized using descriptive statistics (n, mean, standard deviation, minimum and maximum), while gender, race, and other categorical variables were summarized with frequency tabulations. Medical history data were summarized using frequency tabulations. Individual subject listings were also provided.

Efficacy:

The efficacy analysis of the primary endpoint was based on the Full Analysis Set (all subjects who were randomized as specified in the protocol) and repeated using the Per Protocol Population (all subjects who were randomized, received at least 1 dose of IP, had at least 1 postbaseline value for at least 1 of the 7 ACR components, were compliant with study drug, and did not receive prohibited concomitant medications) to determine the robustness of the results.

The primary efficacy endpoint was the ACR 20 assessment at Week 16 (Visit 5) of the Double-blind, Placebo-controlled Treatment Phase. The proportion of subjects randomized to apremilast (either 20 mg BID or 30 mg BID) or placebo who achieved at least an ACR 20 at Week 16 was compared using a two-sided chi-Square test. Subjects who terminated the study prior to Week 16 of the Double-blind, Placebo-controlled Treatment Phase were considered non-responders at Week 16.

Significance testing was done using the following closed procedure: If the overall test among treatments was statistically significant at the 0.05 level, pair-wise comparisons (using a 0.05 two-sided significance level) were to be performed. This procedure maintained the overall significance level at the two-sided 0.05 level.

Secondary endpoints were evaluated sequentially. For each endpoint, statistical significance was declared only if the primary endpoint was significant and the previous secondary endpoints also achieved statistical significance. Significance testing for each parameter was performed using the following closed procedure: if the overall test among treatments was statistically significant at the 0.05 two-sided level, pairwise comparisons (APR 20 mg BID versus PBO, and APR 30 mg BID versus PBO, using a 0.05 two-sided significance level) were performed. Whenever 1 of the pairwise comparisons was not statistically significant at the 0.05 two-sided level, the comparison of placebo versus the dose achieving statistical significance was evaluated using a 0.025 significance level for all subsequent secondary endpoints.

Structure endpoints were to be tested only if the primary endpoint was statistically significant. Adjustment was not performed for these endpoints since the study is a Phase 2 study that was not designed to have adequate power to detect treatment differences.

For planned statistical tests that were not formally performed as a result of the aforementioned multiplicity adjustment strategy, nominal p-values (without adjustment for multiplicity) were still computed as a measure of the strength of the association between the endpoint and the treatment effect, rather than formal tests of hypotheses. In addition, nominal p-values may also have been computed for

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other efficacy analyses, such as supportive or sensitivity analyses of the primary endpoint and those secondary endpoints evaluated at Week 24.

Efficacy endpoints (eg, ACR 20, CDAI, HAQ-DI) for time points beyond 24 weeks were summarized according to the treatment assigned at randomization. For all subjects, changes in measurements were calculated relative to measurements obtained at baseline (Day 1). Data were summarized using descriptive statistics (n, mean, SD, median) for continuous variables and counts and percentages for discrete variables. Two-sided 95% confidence intervals were provided for each treatment group.

Safety:

The safety analyses were performed using the Safety Population (all subjects who were randomized and received at least 1 dose of study drug).

Adverse events were classified using the Medical Dictionary for Drug Regulatory Activities classification system. Adverse events occurring during the Double-blind, Placebo-controlled Treatment Phase; the Double-blind, Active Treatment Phase; the Double-blind, Active Treatment Extension Phase; and the Observational Follow-up Phase were to be tabulated. Treatment-emergent AEs were to be summarized by system organ class, severity, and relationship to investigational product. Adverse events leading to death or to discontinuation from treatment and serious adverse events (SAEs) were also tabulated. In the by-subject analysis, a subject having the same event more than once was counted only once and by greatest severity.

Laboratory data were summarized by visit descriptively. In addition, shift tables showing the number of subjects with values below, within, and above the normal ranges pretreatment versus posttreatment, together with the number determined to be clinically significant, were provided.

Vital sign measurements, including weight, were summarized descriptively by visit (mean, median, standard deviation, minimum and maximum). In addition, shift tables showing the number of subjects with values below, within and above the normal reference ranges pretreatment versus post-treatment, together with the number determined to be clinically significant, were provided.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

As measured by the primary efficacy endpoint of ACR 20 response at Week 16, the study failed to demonstrate statistically significant reduction in the signs and symptoms of RA for either active treatment group compared to placebo.

- The ACR 20 response rates at Week 16 were 35.4% for placebo, 28.0% for APR 20 BID, and 34.2% for APR 30 BID. The difference in the ACR 20 response rates at Week 16 for the APR 20 BID and APR 30 BID dose groups compared to placebo were -7.4% (p = 0.3134) and -1.2% (p = 0.8721), respectively.

Statistical significance could not be declared for any of the key secondary endpoints because the primary endpoint was not met.

- The ACR 20 response rates at Week 24 were 24.1%, 19.5% and 27.6% for placebo,

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APR 20 BID, and APR 30 BID, respectively.

- The ACR 50 response rate at Week 16 and the ACR 70 response rate at Weeks 16 and 24 did not display a treatment or dose effect when comparisons were made between either of the active treatment arms and placebo.
- An ACR 50 response at Week 24 was observed in 6.3% for placebo, in 4.9% for APR 20 BID, and in 15.8% of subjects enrolled in the APR 30 BID group.
- Some subjects may have had a clinical benefit from treatment with APR 30 BID. The mean change in HAQ-DI at Week 16 compared to baseline was -0.106 for the placebo group, -0.114 for the APR 20 BID group, and -0.209 for the APR 30 BID group. At Week 24, the mean change from baseline in HAQ-DI was -0.069, -0.080 and -0.227 for the placebo, APR 20 BID and APR 30 BID dose groups, respectively.
- For secondary endpoints assessed at Week 52, no trends were noted over time or by dose group.

MRI parameters failed to demonstrate a meaningful difference in change from baseline at the Week 16 evaluation for comparisons between the apremilast and the placebo treatment groups.

Radiographic measures of structural damage due to RA remained stable at Week 24 and Week 52 in most subjects treated with apremilast or placebo. For all measures, the changes from Baseline in the APR 20 BID and APR 30 BID treatment groups appeared similar to placebo.

SAFETY RESULTS:

In this study, apremilast administered at unit doses of 20 mg and 30 mg BID with concomitant methotrexate to subjects with rheumatoid arthritis was well tolerated by the majority of subjects.

- The safety profile of apremilast at Week 16, Week 24, and study termination was comparable.
- The majority of subjects in the placebo and apremilast treatment groups reported at least 1 TEAE during the placebo-controlled period, with a higher incidence of TEAEs, which were predominately mild to moderate in severity, among apremilast subjects (51.9% placebo; 67.1% APR 20 BID; and 60.5% APR 30 BID).
- During the placebo-controlled period, the most frequently occurring TEAEs among subjects who received apremilast were nausea, headache, diarrhea, nasopharyngitis, upper abdominal pain, and upper respiratory tract infection.
- Most TEAEs were mild to moderate in severity. Very few subjects in any treatment group experienced severe TEAEs. Two subjects (1 each in the placebo and APR 30 BID treatment

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groups) experienced severe headaches; otherwise, no 2 subjects experienced the same severe TEAE.

- Among subjects who received apremilast, the incidence of TEAEs suspected to be related to IP was approximately twice that of subjects who received placebo. Dose responses were seen for nausea, upper abdominal pain, and decreased appetite.
- In the apremilast-exposure period, the incidence of AEs was similar between the APR 20 BID and APR 30 BID treatment groups (EAIR = 173.9 and 176.5, respectively). Most events were mild or moderate in severity; however, the incidence of severe TEAEs increased in a dose-dependent manner.
- The most frequently reported TEAEs during the apremilast-exposure period were nausea, headache, diarrhea, nasopharyngitis, and upper respiratory tract infection. The EAIR for nausea, headache, and upper respiratory tract infection increased in a dose-dependent manner. No dose effect was observed for diarrhea or nasopharyngitis.
- Two subjects (1 each in the APR 20 BID and APR 30 BID dose groups) reported severe increased blood pressure during the apremilast-exposure period; no other preferred term was reported as severe in more than one subject.
- No subjects died during the study. Few subjects experienced SAEs during the placebo-controlled period. Although SAEs were more frequent in the apremilast treatment groups compared to placebo (and more frequent among APR 30 BID subjects than among APR 20 BID subjects), no preferred term was reported as an SAE by more than one subject.
- During the apremilast-exposure period, a higher EAIR for serious TEAEs was observed in the APR 20 BID treatment group (15.6 per 100 subject-years) compared with the APR 30 BID treatment group (11.4 per 100 subject-years). The preferred terms of appendicitis, transient ischemic attack, and cholelithiasis were each reported as SAEs by 2 subjects. All other serious TEAEs were reported by one subject each.
- In the placebo-controlled period, TEAEs leading to drug interruption and TEAEs leading to drug withdrawal were more common among apremilast subjects. During the apremilast-exposure period, TEAEs leading to drug withdrawal had a higher EAIR among subjects in the APR 30 BID group (19.3 per 100 subject-years) compared with subjects in the APR 20 BID group (11.2 per 100 subject-years). For both the placebo-controlled and apremilast-exposure periods, the only TEAEs leading to withdrawal of more than one subject in a single treatment group were nausea and upper abdominal pain.
- Gastrointestinal AEs were more frequent among apremilast subjects than among placebo subjects, and increased in a dose-dependent manner. Gastrointestinal TEAEs were generally

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mild or moderate in intensity and led to relatively few discontinuations. No clinically meaningful trends were noted in the incidence of infections, malignancies, cardiac events, or the psychiatric events of depression, suicide attempts, or suicidal ideation.

- Three malignancies were reported during the placebo-controlled period (two subjects in APR 20 BID and one subject in APR 30 BID). In addition, two malignancies were reported during the apremilast-exposure period (one subject in placebo/APR 20 BID and one subject in APR 20 BID). No cases of TB or systemic opportunistic infections were reported. *Herpes zoster* was reported in four subjects overall: one subject in the placebo group, 2 subjects in the APR 20 BID group, and one subject in the APR 30 BID group.

CONCLUSION:

This study failed to demonstrate a statistically significant effect for apremilast in reducing the signs and symptoms of RA when administered at unit doses of 20 mg and 30 mg BID, to subjects who were receiving concomitant doses of MTX and who had failed at least 1 prior DMARD, over 16 weeks of study. Apremilast in this setting demonstrated an acceptable toxicity profile, comparable to that observed in earlier studies in subjects with other rheumatic and dermatologic diseases.

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