SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL PA18439)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	**Part A:** A randomized, double-blind, placebo-controlled study to determine the efficacy and safety of 5 dose regimens of RO4402257 in patients with active rheumatoid arthritis on stable methotrexate therapy. **Part B:** A randomized, double-blind, placebo-controlled study to determine the efficacy and safety of 1 dose of RO4402257 in patients with active rheumatoid arthritis on stable methotrexate therapy Report No [redacted] / June, 2008		
INVESTIGATORS / CENTERS AND COUNTRIES	85 investigators in 13 countries (Austria, Brazil, Canada, Estonia, Germany, Great Britain, Greece, Mexico, New Zealand, Poland, South Africa, Spain, United States)		
PUBLICATION (REFERENCE)	Not applicable		
PERIOD OF TRIAL	Part A: Nov 16, 2005 to May 22, 2007 Part B: Aug 6, 2007 to Nov 23, 2007	CLINICAL PHASE	2

OBJECTIVES

The primary objective of the study was to assess the efficacy of RO4402257 in adult patients with rheumatoid arthritis (RA) who had an inadequate clinical response to methotrexate (MTX) therapy.

Secondary objectives were:

1. To assess the safety profile of RO4402257 in patients.
2. To select potentially efficacious and safe dose(s) for future studies.
3. To investigate by a population analysis approach the pharmacokinetics (PK) of RO4402257 in the target RA patient population, including the influence of covariates such as age, gender, and concomitant medications on PK parameters such as the apparent oral clearance (CL/F) and the apparent volume of distribution (V/F).

Additional objectives were:

1. To explore by a population analysis the exposure-response relationship (PK-PD) of RO4402257 in the target RA patient population for the clinical endpoints and the safety parameters.
2. To better understand the efficacy, dose response, safety, and mode of action of RO4402257 and the progression of RA and diseases associated with RA (e.g., osteopenia) through collection and analysis of biomarker samples.

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STUDY DESIGN	Part A: six-arm, randomized, double-blind, placebo-controlled, parallel group study in which patients received placebo in combination with MTX or one of 5 dose regimens of RO4402257 in combination with MTX Part B: two-arm, randomized, double-blind, placebo-controlled, parallel group study in which patients received placebo in combination with MTX or RO4402257 in combination with MTX
NUMBER OF SUBJECTS	Part A: Planned: 330 (approximately 55 per treatment group) Placebo + MTX, 53 RO4402257 25 mg twice daily (BID) + MTX, 57 RO4402257 75 mg BID + MTX, 57 RO4402257 50 mg once daily (QD) + MTX, 53 RO4402257 150 mg QD + MTX, 53 RO4402257 300 mg QD + MTX, 54 Part B: Planned: 110 (approximately 75 in the RO4402257 treatment group and 35 in the placebo treatment group) Placebo + MTX, 12 RO4402257 150 mg BID +MTX, 23 The study was terminated prematurely.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with active RA who were receiving MTX for at least 24 weeks and had an inadequate clinical response to MTX therapy
TRIAL DRUG / STROKE (BATCH) No.	RO4402257 tablets / formulations provided in Study Documentation
DOSE / ROUTE / REGIMEN / DURATION	Part A: 25 mg BID: one 25-mg RO4402257 tablet every morning and every evening 75 mg BID: one 75-mg RO4402257 tablet every morning and every evening 50 mg QD: two 25-mg RO4402257 tablets every morning 150 mg QD: two 75-mg RO4402257 tablets every morning 300 mg QD: two 150-mg RO4402257 tablets every morning Treatment was for 12 weeks Part B: 150 mg BID: one 150-mg RO4402257 tablet every morning and every evening
REFERENCE DRUG / STROKE (BATCH) No.	Placebo tablets / formulations provided in Study Documentation

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DOSE / ROUTE / REGIMEN / DURATION	Part A: 25 mg BID: one placebo tablet every morning and one placebo tablet every evening 75 mg BID: one placebo tablet every morning and one placebo tablet every evening 50 mg QD: two placebo tablets every evening 150 mg QD: two placebo tablets every evening 300 mg QD: two placebo tablets every evening Placebo: two placebo tablets every morning and two placebo tablets every evening Part B: Placebo: one placebo tablet every morning and one placebo tablet every evening
CRITERIA FOR EVALUATION	
EFFICACY:	Primary: proportion of patients with an American College of Rheumatology 20 (ACR20) response at week 12 Secondary: 1. Proportion of patients with ACR50 responses at Week 12 2. Proportion of patients with ACR70 responses at Week 12 3. Proportion of patients with ACR patient questionnaire subset response 4. Change from baseline in the individual ACR core set parameters 5. Change from baseline in disease activity score (DAS28) 6. Categorical analyses of DAS28 7. SF-36 assessment 8. FACIT-F fatigue assessment 9. Proportion of patients who withdraw due to insufficient therapeutic response
PHARMACODYNAMICS:	Biomarkers associated with inflammation and bone development
PHARMACOKINETICS:	Plasma samples were collected for pharmacokinetic analysis of RO4402257 and its metabolites. Results are not presented in this abbreviated report.
SAFETY:	Adverse events (AEs), laboratory abnormalities, immunology assessments, electrocardiograms (ECGs), and vital signs
STATISTICAL METHODS	All patients who received study drug were included in the primary efficacy analysis and the safety analysis. Patients who withdrew from the study prior to the week 12 assessment were considered

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nonresponders for the primary efficacy analysis. Results for efficacy and safety parameters are presented using descriptive statistics.

METHODOLOGY:

After a screening period of up to 3 weeks, eligible patients were randomly assigned to one of the treatment groups in Part A or Part B of the study and received 12-weeks of double-blind treatment. Efficacy assessments and safety laboratory assessments were made at baseline (prior to first dose of study medication) and at weeks 1, 2, 4, 8, and 12 (or early termination). Adverse events and laboratory abnormalities, particularly those considered to be drug-related, were followed until resolution or stabilization. All patients were required to return for a safety follow up visit approximately 4 weeks after their last dose of study medication.

EFFICACY RESULTS:

For Part A of the study, the percentage of patients with an ACR20 response at week 12 was approximately 10% higher in several of the RO4402257 treatment groups compared to the placebo treatment group; however, these differences were not statistically significant.

PHARMACODYNAMIC RESULTS:

Little or no change was observed in either the inflammatory or bone development biomarkers.

SAFETY RESULTS:

In each treatment group, most AEs were mild. The most frequent AEs in the RO4402257 treatment groups in Part A of the study were dizziness and nasopharyngitis. Headache, tremor, and nausea were the only AEs in Part B in the RO4402257 treatment group reported by more than one patient (2 patients each).
The percentage of patients with a serious AE was higher in the RO4402257 treatment groups than in the placebo treatment group during Part A of the study. Eight patients (all in the RO4402257 treatment groups) had serious AEs that the investigator considered related to study medication; these events were streptococcal sepsis, supraventricular tachycardia, rheumatoid arthritis, cellulitis, vomiting, gastrointestinal hemorrhage, pneumonia, and visual disturbance. No serious AEs were reported during Part B. The percentage of patients having AEs and laboratory abnormalities leading to withdrawal was higher in the RO4402257 treatment groups than in the placebo treatment group in Part A of the study. One patient in the RO4402257 treatment group withdrew because of an AE during Part B.
There was no evidence of a QT prolongation with RO4402257.
There were no clinically significant changes from baseline in any of the immunology test parameters.

CONCLUSIONS:

RO4402257 showed an approximately 10% increase in efficacy in comparison with placebo, a difference that was not statistically significant. At the highest doses tested (300 mg QD; 150 mg BID), RO4402257 in combination with MTX was less well tolerated than MTX plus placebo.