SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL PA18604)

COMPANY: F. Hoffmann-La Roche Ltd., Basel NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): RO4402257	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized, double-blind, double-dummy, parallel group study to determine the efficacy and safety of RO4402257 monotherapy in comparison to methotrexate monotherapy in patients with active rheumatoid arthritis (RA)/ Report No. [redacted] / December 2007		
INVESTIGATORS / CENTERS AND COUNTRIES	A total of 61 centers in 12 countries (Canada, Croatia, Czech Republic, France, Italy, Mexico, Romania, Serbia/Montenegro, South Africa, Spain, Taiwan, United States)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	February 9, 2006 to June 21, 2007	CLINICAL PHASE	II
OBJECTIVES	To assess the efficacy and safety of 3 dose levels of RO4402257 as monotherapy in adult patients with active RA		
STUDY DESIGN	Four-arm, randomized, double-blind, double-dummy, parallel group study in which patients received methotrexate (MTX) or one of 3 dose regimens of RO4402257		
NUMBER OF SUBJECTS	Planned: 200 (approximately 50 per treatment group) Enrolled: MTX, 53 RO4402257 50 mg QD, 52 RO4402257 150 mg QD, 51 RO4402257 300 mg QD, 48		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with active RA who were not currently receiving MTX or other disease-modifying anti-rheumatic drugs (DMARDs) and had an inadequate clinical response to their current anti-inflammatory therapy		
TRIAL DRUG / STROKE (BATCH) No.	RO4402257 tablets 25 mg (formulation 440-2257/F11): [redacted] 75 mg (formulation 440-2257/F12): [redacted] 150 mg (formulation 440-2257/F13): [redacted] MTX placebo capsule (formulation 002-9893/F03): [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	50 mg once daily (QD): two 25-mg RO4402257 tablets + MTX placebo weekly for 12 weeks 150 mg QD: two 75-mg RO4402257 tablets + MTX placebo weekly for 12 weeks 300 mg QD: two 150-mg RO4402257 tablets + MTX placebo weekly for 12 weeks		
REFERENCE DRUG / STROKE (BATCH) No.	MTX 2.5-mg tablet in capsule (formulation 002-9893/F01): [redacted] RO4402257 placebo (formulation 440-2257/F14): [redacted]		

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DOSE / ROUTE / REGIMEN / DURATION	RO4402257 placebo (2 tablets QD) + 7.5 to 20 mg MTX weekly in ascending doses for 12 weeks. Starting dose was 7.5 mg weekly. At end of week 4, all patients were to be instructed to take 15 mg PO weekly. At end of week 8, dose could be increased to 20 mg if patient had painful or swollen joints without significant MTX-related toxicity.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary:** proportion of patients with an ACR20 response at week 12 **Secondary:** change from baseline in the individual ACR core set parameters, other efficacy parameters as defined in the protocol
PHARMACODYNAMICS:	Biomarkers associated with inflammation and bone development were assessed.
PHARMACOKINETICS:	Plasma samples were collected for pharmacokinetic analysis of RO4402257 and metabolites. Results not presented in this abbreviated report.
SAFETY:	Adverse events (AEs), laboratory abnormalities, immunology assessments, electrocardiograms (ECGs), vital signs
STATISTICAL METHODS	All patients who received study drug were included in the primary efficacy analysis. Patients who withdrew from the study prior to the week 12 assessment were considered non-responders for the primary 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 4 treatment groups 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:

The percentages of patients with ACR20 and ACR50 response at week 12 were lower in each of the three RO4402257 groups than in the MTX group, as shown in the following table. The percentage with ACR20 response at week 12 was higher in the 300 mg QD group than in the other two RO4402257 groups.

Parameter	**MTX (N = 53)**	**50 mg QD (N = 52)**	**150 mg QD (N = 51)**	**300 mg QD (N = 48)**
ACR20	53%	29%	21%	39%
ACR50	27%	14%	7%	16%

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PHARMACODYNAMIC RESULTS:

For the inflammatory markers CRP and IL-6, increased levels over time were noted in some patients randomized to the RO4402257 300 mg treatment group. Little or no change was observed in the bone markers ßCTx (the marker of type v1 collagen degradation), osteocalcin (the marker of bone metabolism), and PTH (the key marker of calcium metabolism). For PNP-1, the marker of type 1 collagen synthesis, increases were observed in all treatment groups except RO4402257 50 mg QD.

SAFETY RESULTS:

In each treatment group, most AEs were mild. The percentage having severe AEs ranged from 2% in the RO4402257 50 mg QD group to 12% in the RO4402257 150 mg QD group. The most frequent AEs in the RO4402257 groups were dizziness, hepatic enzyme increased, upper respiratory tract infection, and constipation.

The percentages of patients having serious AEs were higher in the RO4402257 150 mg and 300 mg groups (8% and 10%, respectively) than in the MTX and RO4402257 50 mg groups (4% and 2%, respectively). Four patients (all in RO4402257 groups) had serious AEs that the investigator considered related to study medication: pneumonia, gastrointestinal hemorrhage, sialoadenitis, and gastrointestinal infection. The percentage of patients having AEs and laboratory abnormalities leading to withdrawal was higher in the RO4402257 300 mg QD group (21%) than in the other 3 treatment groups (6% to 8%).

The following shifts in laboratory values were observed in all 4 treatment groups: decreases in hemoglobin; increases in ASAT, ALAT, alkaline phosphatase, CPK, and triglycerides.

In ECGs, there was no evidence of QT prolongation with RO4402257.

There were no clinically significant changes from baseline in any of the immunology test parameters.

CONCLUSIONS:

RO4402257 showed lower efficacy in comparison with MTX. At the highest dose tested (300 mg QD), RO4402257 was less well-tolerated than MTX.