SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, LLC
Name of Finished Product	RWJ-445380
Name of Active Ingredient(s)	Not applicable

Protocol No.: C-2006-009-03

Title of Study: A Phase IIa Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of RWJ-445380 Cathepsin-S Inhibitor in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy

Coordinating Investigator: A coordinating investigator was not assigned for this study (see Appendix 1.4.1 for a list of investigators).

Publication (Reference): None

Study Period: 12 December 2006 to 15 January 2008

Phase of Development: 2a

Objectives: Primary: To assess the safety and tolerability of RWJ-445380 with daily doses of 100, 200, or 300 mg for up to 12 weeks in patients with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy. Secondary: To evaluate the efficacy of RWJ-445380 in patients with active RA despite MTX therapy receiving daily doses of 100, 200, or 300 mg; and to assess the effect of RWJ-445380 on various biomarkers associated with RA.

Methods: This was a randomized, double-blind, placebo-controlled, multicenter, parallel group study that evaluated RWJ-445380 in patients with RA. Men and women aged 18 years or older with active RA (per American College of Rheumatology [ACR] criteria) for at least 6 months despite MTX therapy were enrolled. Approximately 60 patients were assigned to each of 4 treatment groups to receive placebo or RWJ-445380 100, 200, or 300 mg/day for 12 weeks. There was a 4-week follow-up period after dosing was completed.

Number of Patients (planned and analyzed): 240 planned, 422 screened, 259 enrolled, and 214 completed the study.

Diagnosis and Main Criteria for Inclusion: Patients were 18 years of age or older with active RA for at least 6 months. Patients must have been on MTX for at least 6 months with a stable dose of 10 to 25 mg/week for a minimum of 8 weeks. Patients may have been taking oral corticosteroids if the dose was ≤10 mg/day prednisone (or equivalent corticosteroid) and had not been changed for a minimum of 4 weeks. Patients must not have had more than one prior treatment with, or had been currently taking, anti-tumor necrosis factor (TNF) agents (eg, infliximab, etanercept, or adalimumab) and must not have had prior or current therapy with abatacept, rituximab, cytotoxic agents, or Prosorba® column.

Test Product, Dose, and Mode of Administration, Lot No.:
RWJ-445380 100 mg/day, oral (two 50-mg capsules, lot numbers: R14273 and R14376)
RWJ-445380 200 mg/day, oral (two 100-mg capsules, lot numbers: R14274 and R14377)
RWJ-445380 300 mg/day, oral (two 150-mg capsules, lot numbers: R14275 and R14378)

Reference Therapy, Dose, and Mode of Administration, Lot No.:
Placebo, oral (lot numbers: R14276 and R14379)

Duration of Treatment: The duration of treatment was 12 weeks with a 4-week follow-up period.

Criteria for Evaluation: Efficacy was assessed by RA response joint assessments (Swollen Joint Count [SJC] and Tender Joint Count [TJC]) (at screening, day 0, weeks 4 and 8, termination, and follow-up), C-reactive protein (CRP), patient assessment of physical function, patient assessment of pain, patient global assessment of disease activity (Health Assessment Questionnaire Disability Index [HAQ-DI]), and evaluator global assessment of disease activity (at day 0, weeks 4 and 8, termination, and follow-up).

Pharmacokinetic parameters were assessed by measurement of plasma concentrations of RWJ-445380 in samples drawn at weeks 4 and 8 and termination. Pharmacodynamic parameters included Iip10 accumulation in peripheral blood mononuclear cells (at day 0, weeks 4 and 8, termination, and follow-up) and antibody response to the tetanus toxoid booster immunization administered at week 6 (testing at weeks 4 and 8 and termination). Other assessments included serum biomarkers (at day 0, weeks 4 and 8, termination, and follow-up) and genotyping (at day 0). Participation in genotyping was not mandatory for participation in the study.

Safety was assessed by adverse event and concomitant therapy monitoring throughout the study; clinical laboratory tests (hematology, chemistry, and urinalysis; at screening, day 0, weeks 1, 2, 4, 6, and 8, termination, and follow-up); vital sign measurements (at screening, day 0, weeks 1, 2, 4, 6, 8, and 10, termination, and follow-up); physical examinations (at screening and termination); electrocardiogram (ECG) findings (at screening, day 0, weeks 1, 2, 4, and 8, and termination); pregnancy tests for women of childbearing potential (at screening, day 0, weeks 4 and 8, and termination); hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, anti-hepatitis C virus antibody, anti-human immunodeficiency virus antibody, and tuberculosis testing (skin test) (at screening).

Statistical Methods: Efficacy Analysis: All evaluable patients with at least 1 qualifying post baseline measurement were included in the efficacy analysis. Evaluable patients were defined as those that had received study drug and had at least 1 efficacy evaluation before any possible change in concomitant therapy for treatment of RA as defined by the protocol. Qualifying post baseline measurement was defined as any measurement after randomization and before any possible change in concomitant medications for treatment of RA. Study endpoint was defined as the last available qualifying post baseline measurement. In addition, ACR response was analyzed at "alternative study endpoint"; this endpoint considered any patient that discontinued the study early as an ACR non-responder regardless of their last available qualifying post baseline measurement.

Descriptive statistics were calculated for all efficacy parameters. The primary efficacy parameter was ACR20 response at study endpoint and was analyzed using a chi-square test of equal proportions among the 4 treatment groups. Testing was performed for each active treatment group against placebo. This same procedure was used for ACR50 and ACR70 response. Percentage ACR improvement was analyzed using an analysis of variance model including treatment as the main effect. Other efficacy parameters were analyzed using an analysis of covariance model with treatment as the main effect and baseline score as the covariate.

Pharmacokinetic, Pharmacodynamic, and Other Analyses: Plasma concentration data and tetanus toxoid data were tabulated. Serum biomarker, Iip10, and genotyping analyses are discussed in a separate report.

Safety: All patients who received treatment with study drug were included in safety analysis. Termination data, adverse events, vital sign measurements, concomitant therapy, ECG results, physical examination findings, clinical laboratory results, and itch assessment data were tabulated and summarized. Adverse events were coded in the Medical Dictionary for Regulatory Activities® (MedDRA®).

RESULTS:

Two hundred fifty-nine (259) patients were enrolled in 7 countries, and 214 (82.6%) patients completed the study. Treatment distribution was balanced at randomization, but more patients

discontinued early in the 100, 200, and 300 mg treatment groups than in the placebo group. Overall, the most common reason for discontinuation was adverse event.

Patient Disposition (All Randomized Patients)

		RWJ-445380			
	Placebo (n=65)	100 mg (n=66)	200 mg (n=67)	300 mg (n=61)	Total (N=259)
Received study treatment	65 (100%)	66 (100%)	67 (100%)	61 (100%)	259 (100%)
Completed study treatment	59 (90.8%)	54 (81.8%)	56 (83.6%)	45 (73.8%)	214 (82.6%)
Discontinued study treatment early	6 (9.2%)	12 (18.2%)	11 (16.4%)	16 (26.2%)	45 (17.4%)
Reasons for early discontinuation					
Adverse event	1 (16.7%)	4 (33.3%)	8 (72.7%)	11 (68.8%)	24 (53.3%)
Protocol violation	1 (16.7%)	1 (8.3%)	0	0	2 (4.4%)
Personal reason	0	0	0	1 (6.3%)	1 (2.2%)
Lack of efficacy	2 (33.3%)	4 (33.3%)	2 (18.2%)	1 (6.3%)	9 (20.0%)
Lost to follow-up	0	1 (8.3%)	0	2 (12.5%)	3 (6.7%)
Withdrawal of consent	0	1 (8.3%)	1 (9.1%)	1 (6.3%)	3 (6.7%)
Other	2 (33.3%)	1 (8.3%)	0	0	3 (6.7%)

Note: Two patients discontinued due to an adverse event that started before randomization and was not treatment emergent.

Demographic and baseline disease characteristics were similar among treatment groups. Mean patient age was 50.3 years (range: 22 to 85 years) and mean patient weight was 71.3 kg. Most patients were women (83.4%) and white (79.2%), and over half (59.8%) of patients were Hispanic. The mean and median times since RA diagnosis were 8.3 and 6.1 years, respectively. The majority (68.6%) of patients was categorized as Functional Class II, and 9.3% of patients reported past use of anti-TNF agents.

EFFICACY RESULTS: No significant differences across treatment groups were seen in any of the efficacy endpoints, including the primary efficacy parameter of ACR20 at study endpoint and the secondary efficacy parameters of ACR50, ACR70, percentage ACR improvement, and DAS28-4(CRP). In addition, there was no statistically significant difference in ACR20 response at study endpoint across treatment groups when analyzed by geographic region (ie, North America, South America/Mexico, and Europe).

Summary of Efficacy Measurements at Study Endpoint

Efficacy Measurements	Placebo (n=65)	RWJ-445380 100 mg (n=66)	RWJ-445380 200 mg (n=67)	RWJ-445380 300 mg (n=61)	p value
ACR20	23 (35.4%)	33 (51.6%)	23 (34.8%)	26 (43.3%)	0.1750
ACR50	14 (21.5%)	10 (15.6%)	13 (19.7%)	14 (23.3%)	0.7334
ACR70	6 (9.2%)	4 (6.3%)	3 (4.5%)	8 (13.3%)	0.2992
% ACR improvement[a]	21.81 (27.77)	23.29 (25.30)	19.16 (24.91)	25.01 (29.67)	0.6575
DAS28-4(CRP)[a]	4.56 (1.55)	4.43 (1.49)	4.56 (1.41)	4.48 (1.51)	0.7235
TJC (0-68)[a]	16.55 (18.01)	16.66 (14.87)	17.68 (15.59)	16.73 (15.30)	0.8927
SJC (0-66)[a]	10.28 (11.60)	9.91 (10.31)	9.27 (8.03)	10.32 (9.51)	0.8369
Patient global assessment of disease activity[a]	41.98 (25.11)	40.23 (26.60)	43.95 (24.48)	39.23 (27.92)	0.3701
Patient assessment of pain[a]	45.44 (25.89)	41.56 (27.81)	42.55 (25.84)	37.92 (26.72)	0.0924
Evaluator global assessment of disease activity[a]	37.68 (26.07)	35.14 (24.72)	35.56 (21.94)	33.43 (24.58)	0.6544
CRP[a]	13.88 (16.63)	12.50 (16.23)	13.67 (22.99)	11.89 (15.52)	0.7947
HAQ-DI[a]	1.18 (0.83)	1.16 (0.69)	1.14 (0.75)	1.12 (0.67)	0.7038

[a] Values are mean (standard deviation).

Note: p value is based on overall comparison of all treatments. For ACR response, a chi-squared test was used. For percentage ACR improvement, an analysis of variance model with treatment as the main effect was used. For other measurements, an analysis of covariance model was used with treatment as the main effect and baseline score as the covariate.

ACR = American College of Rheumatology; CRP = C-reactive protein; DAS28-4(CRP) = Disease Activity Index Score 28 CRP; HAQ-DI = Health Assessment Questionnaire Disability Index; SJC = Swollen Joint Count; TJC = Tender Joint Count.

PHARMACOKINETIC, PHARMACODYNAMIC, AND OTHER RESULTS: Pharmacokinetic data are presented in attachments, but are not discussed in this report. Serum biomarker, Iip10, and pharmacogenomic results are presented in separate reports.

Antibody response to the tetanus toxoid booster immunization given during the study was measured to assess any impact on recall (memory) immune function. Approximately half of the patients in each treatment group demonstrated a response to immunization with at least a fourfold increase in titer. Results suggest that there is no apparent blocking of the immune response to this recall antigen in patients treated with RWJ-445380 within the dose range administered during the study.

SAFETY RESULTS: A higher proportion of patients in the 200 and 300 mg treatment groups (82.1% [55/67 patients] and 77.0% [47/61 patients], respectively) reported at least 1 treatment-emergent adverse event compared with the placebo and 100 mg groups (53.8% [35/65 patients] and 68.2% [45/66 patients], respectively). There was a higher proportion of patients who discontinued study drug due to treatment-emergent adverse events in RWJ-445380 treatment groups compared with the placebo group, and there also appeared to be a dose-related effect (see following table).

Seven serious adverse events were reported in 5 patients: 2 patients in the placebo group (hepatitis and thrombosis) and 3 patients in the 200 mg group (ovarian abscess with reactive appendicitis, appendicitis, and bronchitis with hypoxemic cardiac ischemia). No patients had serious adverse events in the 100 and 300 mg groups. One death in the 200 mg group was reported. This patient experienced a serious adverse event of bronchitis for which she received levofloxacin. Two days later, she discontinued study drug due to lack of efficacy. The following day, the patient was found dead in her bed with the cause of death reported by the investigator as hypoxemic cardiac ischemia.

Summary of Treatment-Emergent Adverse Events (All Randomized Patients)

	Placebo (n=65)	RWJ-445380 100 mg (n=66)	RWJ-445380 200 mg (n=67)	RWJ-445380 300 mg (n=61)	Total (N=259)
Number (%) of patients with at least 1					
Adverse event	35 (53.8%)	45 (68.2%)	55 (82.1%)	47 (77.0%)	182 (70.3%)
Severe adverse event	4 (6.2%)	1 (1.5%)	9 (13.4%)	9 (14.8%)	23 (8.9%)
Serious adverse event	2 (3.1%)	0	3 (4.5%)	0	5 (1.9%)
Adverse event resulting in early termination	1 (1.5%)	3 (4.5%)	8 (11.9%)	10 (16.4%)	22 (8.5%)

Note: Adverse events summarized in this table are those with onset at or after randomization and before 30 days after study drug discontinuation.

The most common treatment-emergent adverse event was pruritus. There was a higher proportion of patients reporting pruritus in the 200 and 300 mg treatment groups compared with the placebo and 100 mg groups (see following table). Pruritus was the most frequent cause of study drug discontinuation in patients receiving 200 or 300 mg RWJ-445380, with occurrence being dose related: 0, 1.5% (1/66 patients), 9.0% (6/67 patients), and 13.1% (8/61 patients) of patients in the placebo and 100, 200, and 300 mg treatment groups, respectively. Pruritus was more likely to be reported as severe and described as "constant", "generalized", and/or "affecting sleep" by patients receiving RWJ-445380 than by patients receiving placebo.

Increased alanine aminotransferase (ALT) was reported by 1.5% (1/65 patients), 0, 7.5% (5/67 patients), and 11.5% (7/61 patients) of patients in the placebo and 100, 200, and 300 mg treatment groups, respectively. One patient in the 300 mg group discontinued study drug due to increased ALT, and only 1 hepatic event constituted a serious adverse event (hepatitis in a placebo-treated patient).

Treatment-Emergent Adverse Events Reported by >5% of Patients Within One or More Treatment Groups (All Randomized Patients)

	Placebo (n=65)	RWJ-445380 100 mg (n=66)	RWJ-445380 200 mg (n=67)	RWJ-445380 300 mg (n=61)	Total (N=259)
Gastrointestinal disorders					
Diarrhea	2 (3.1%)	4 (6.1%)	0	1 (1.6%)	7 (2.7%)
Infections and infestations					
Upper respiratory tract infection	1 (1.5%)	4 (6.1%)	1 (1.5%)	3 (4.9%)	9 (3.5%)
Investigations					
Alanine aminotransferase increased	1 (1.5%)	0	5 (7.5%)	7 (11.5%)	13 (5.0%)
Nervous system disorders					
Headache	5 (7.7%)	1 (1.5%)	4 (6.0%)	3 (4.9%)	13 (5.0%)
Skin and subcutaneous tissue disorders					
Pruritus	13 (20.0%)	15 (22.7%)	35 (52.2%)	34 (55.7%)	97 (37.5%)
Vascular disorders					
Hypertension	2 (3.1%)	4 (6.1%)	1 (1.5%)	1 (1.6%)	8 (3.1%)

Note: A patient may be reported in more than 1 system organ class. Adverse event mapping was based on the Medical Dictionary for Regulatory Activities® (MedDRA®).

Increases in serum ALT to >3 × upper limit of normal (ULN) were reported in 2 (3.1%), 1 (1.5%), 1 (1.5%), and 7 (11.5%) patients in the placebo and 100, 200, and 300 mg treatment groups, respectively. For all treatment groups, there was a greater proportion of patients with ALT increased >2 × ULN during the study who had increased ALT values at baseline compared with patients who had normal ALT levels at baseline.

Treatment with RWJ-445380 did not appear to be associated with an increase in infections or prolongation in QT interval.

CONCLUSION: The results of this study indicate that RWJ-445380 at dosages of 100, 200, and 300 mg/day was not effective in the treatment of patients with active RA despite MTX therapy. Except for the adverse events of pruritus and elevated ALT, RWJ-445380 was well tolerated at all 3 dosages.

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