A 24-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy of Oral SCIO-469, a p38 Mitogen-activated Protein Kinase Inhibitor, in Patients with Active Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the efficacy, safety, and tolerability of oral SCIO-469, a p38 MAPK inhibitor that blocks tumor necrosis factor-α, interleukin-1ß, and cyclooxygenase-2 synthesis in patients with active rheumatoid arthritis (RA).

Methods. Patients were randomized to receive SCIO-469 at either 30 or 60 mg three times daily in an immediate-release (IR) formulation or at 100 mg once daily in an extended-release (ER) formulation, or placebo for 24 weeks. The primary endpoint was American College of Rheumatology (ACR)20 response at Week 12. Safety was monitored through Week 26.

Results. Overall, 302 patients were randomized: 76 to placebo, 75 to 30 mg IR, 73 to 60 mg IR, and 78 to 100 mg ER. There were no significant differences in ACR20 responses at Week 12 between SCIO-469 and placebo. Declines in C-reactive protein and erythrocyte sedimentation rate during early treatment did not persist to Week 12 and were not a consequence of decreased SCIO-469 plasma levels. The 60 mg IR regimen showed a dose-limiting toxicity manifested by elevations in alanine aminotransferase. Adverse events were common in all groups (79.7% and 86.7% through 13 and 26 weeks, respectively). Twenty-one patients reported 28 serious adverse events (SAE). SAE were more common with IR SCIO-469 than with placebo (7% vs 4%) but were not reported with ER SCIO-469.

Conclusion. In all regimens tested, SCIO-469 showed no greater efficacy compared to placebo in patients with RA. The transient effect of SCIO-469 on acute-phase reactants suggests a complex role of p38 MAPK in inflammation. (J Rheumatol First Release Feb 1 2011; doi:10.3899/jrheum.100602)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by joint swelling and tenderness, joint damage, bone destruction, and cartilage loss, and can result in significant disability. Cytokines, including tumor necrosis factor (TNF-α) and interleukin (IL)-1, promote chronic inflammation and are important mediators in the pathogenesis of RA[1]. Currently indicated biological therapies that inhibit TNF-α, and IL-1, IL-6, T cell costimulation, and B-cell survival can reduce the signs and symptoms of RA and joint damage in some patients[2,3,4]. These therapies, which must be administered by either intravenous infusion or subcutaneous injection, can be associated with serious adverse events (SAE), and are often more expensive than small-molecule oral agents. Therefore, there is a considerable need for new small-molecule pharmacologic therapies to treat RA.

A key regulator of proinflammatory cytokine production is p38 mitogen-activated protein kinase (MAPK), and phosphorylation of p38 MAPK results in the transcriptional activation of TNF-α, IL-1, and IL-6[5,6]. The phosphorylated, activated form of p38 MAPK has been isolated from the synovial lining and endothelial cells of synovial microvessels in patients with RA[7]. Several studies have shown that inhibition of p38 MAPK also suppresses the production of TNF-α, IL-1, and IL-6[8]. In addition, suppression of p38 MAPK activity reduced both paw swelling and joint damage in rat models of RA[6,9]. Therefore, compounds that inhibit p38 MAPK may have therapeutic benefit for patients with RA.

SCIO-469 is an orally administered active inhibitor of p38-α MAPK, i.e., p38-α inhibitor that blocks the synthesis of TNF-α and IL-1ß. In rats with established experimental arthritis, SCIO-469 reduced signs and symptoms of disease and slowed disease progression. SCIO-469 was well tolerated in phase I testing[10]. Here we report the efficacy and safety results of a phase II, randomized, placebo-controlled trial of SCIO-469 in patients with active RA who were not on methotrexate or biologic response modifiers.

MATERIALS AND METHODS

Patients. Eligible patients were ≥ 18 years of age; met the revised 1987 American Rheumatism Association (now American College of Rheumatology; ACR) criteria for RA[11]; and had ≥ 9 tender joints, ≥ 6 swollen joints; and either a C-reactive protein (CRP) level ≥ 1.0 mg/dl, an erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, or morning stiffness for ≥ 45 min. Patients were excluded from the study if they met any of the criteria for RA functional class IV[12] (limited ability to perform usual self-care and vocational/avocational activities) or were taking any of the following RA medications before study-agent administration: leflunomide within 10 weeks, any experimental biologic response modifier or infliximab within 8 weeks, or any other disease-modifying antirheumatic drug (DMARD) within 4 weeks, except stable-dose hydroxychloroquine, chloroquine, minocycline, and doxycycline. The protocol was approved by the institutional review board at each study site. All patients provided written informed consent.

Study design and evaluations. In this double-blind, placebo-controlled, parallel-group study, patients were randomly assigned by an interactive voice response system (IVRS) in a 1:1:1:1 ratio to receive SCIO-469 30 mg immediate release (IR) three times daily (tid), SCIO-469 60 mg IR tid, SCIO-469 100 mg extended release (ER) once daily (qd), or placebo for 24 weeks. A followup visit occurred at Week 26.

The primary efficacy endpoint was the percentage of patients who achieved a 20% improvement in the ACR20 criteria[13], comprising the 68 tender joint count and 66 swollen joint count, Health Assessment Questionnaire (HAQ), visual analog scale for pain, patient global assessment, physician global assessment, and acute-phase reactant CRP/ESR at Week 12. Secondary endpoints were ACR50 (≥ 50% improvement in ACR criteria) response at Week 12; ACR20 and ACR50 responses at each study visit other than week 12; Disease Activity Score (DAS)28, and mean changes in all components of the ACR response criteria at each study visit.

At Week 13, patients who did not achieve a modified ACR20 response (excluding CRP and ESR tests) were considered nonresponders and were reassigned by an IVRS (which maintained the double-blind status for all patients) to an alternative treatment regimen, as follows: those initially assigned to placebo were switched to 30 mg SCIO-469 IR tid; those initially assigned to SCIO-469 30 mg IR tid were switched to 60 mg IR tid; and those initially assigned to SCIO-469 100 mg ER qd were switched to 30 mg IR tid. Patients receiving 60 mg IR tid were not reassigned.

Safety assessments monitored throughout the entire study period included adverse events (AE), clinical laboratory evaluations, physical examinations, vital signs, and 12-lead electrocardiograms.

Blood samples were collected pre-study-agent administration at Day 1 and weeks 1, 2, 4, 8, 12, 13, 14, 16, 20, and 24 for analysis of trough plasma levels of SCIO-469 and its 2 major metabolites, M1 and M2, by a validated liquid chromatography tandem mass spectrometry assay.

In addition, whole blood samples from the first 120 subjects who enrolled in the study were collected at pre-study-agent administration on Day 1 and weeks 1, 4, 12, and 26 for biomarker analysis of serum levels of IL-6, IL-1R-α (as a surrogate for IL-1ß), IL-8, intercellular adhesion molecule (ICAM)-1, and matrix metalloproteinase (MMP)-3. Assays were performed only for patients who had a baseline CRP of 0.8 mg/dl or higher and had evaluable samples at baseline and at least 1 post-baseline visit.

Concomitant medications. The use of low-dose prednisone (≤ 10 mg/d up to Week 24 and ≤ 20 mg/d between weeks 24 and 26), nonsteroidal antiinflammatory drugs (NSAID; up to 125% the recommended dose), and cyclooxygenase (COX)-2 inhibitors were allowed during the study if patients were receiving stable doses for ≥ 4 weeks before the first study-drug administration. The use of hydroxychloroquine, chloroquine, minocycline, and doxycycline was permitted during the study if the doses were stable for ≥ 12 weeks before the first study-drug administration. One intraarticular steroid injection was permitted during the first 60 d, if the affected joint was scored as active (both swollen and tender) for the next 30 d, and was permitted after the first 60 d, and if the affected joint was scored as active for the remainder of the study. Analgesic and antiinflammatory agents, including NSAID and COX-2 inhibitors, could not be taken within 12 hours before efficacy evaluations.

Statistical analysis. Descriptive statistics, including means, SD, and SE for continuous variables and counts and percentages for discrete variables, were used to summarize the data. For the primary efficacy analysis at Week 12, ACR responses were calculated using a nonresponder imputation; any patients who received prohibited concomitant therapies were considered nonresponders. Last-observation-carried-forward imputation was used to handle missing values up to Week 12. Differences in the proportion of ACR20 responders at Week 12 between each active treatment group and placebo were evaluated using Dunnett's modification for the chi-squared test.

RESULTS

Patient disposition. Between July 2004 and October 2005, 302 patients were randomly assigned to receive study treatment (Figure 1) at 48 study sites in the United States. One patient assigned to receive SCIO-469 30 mg IR tid withdrew from the study prior to treatment initiation and was excluded from the analysis. Similar percentages of patients in each group discontinued study treatment or study participation by Week 13 (Figure 1). In general, a higher percentage of responders than nonresponders completed the study.

Baseline characteristics. Demographic characteristics at baseline were similar among treatment groups (Table 1). The population was predominantly women (80%) and white (78%), with a mean age of 54 years. Disease characteristics were comparable among treatment groups (Table 1).

Concomitant medications. At baseline, the percentages of patients reporting prior use of prednisone (125/301; 42%), COX-2 inhibitors/NSAID (154/301; 51%), and DMARD (215/301; 71%) that were prohibited during the study were

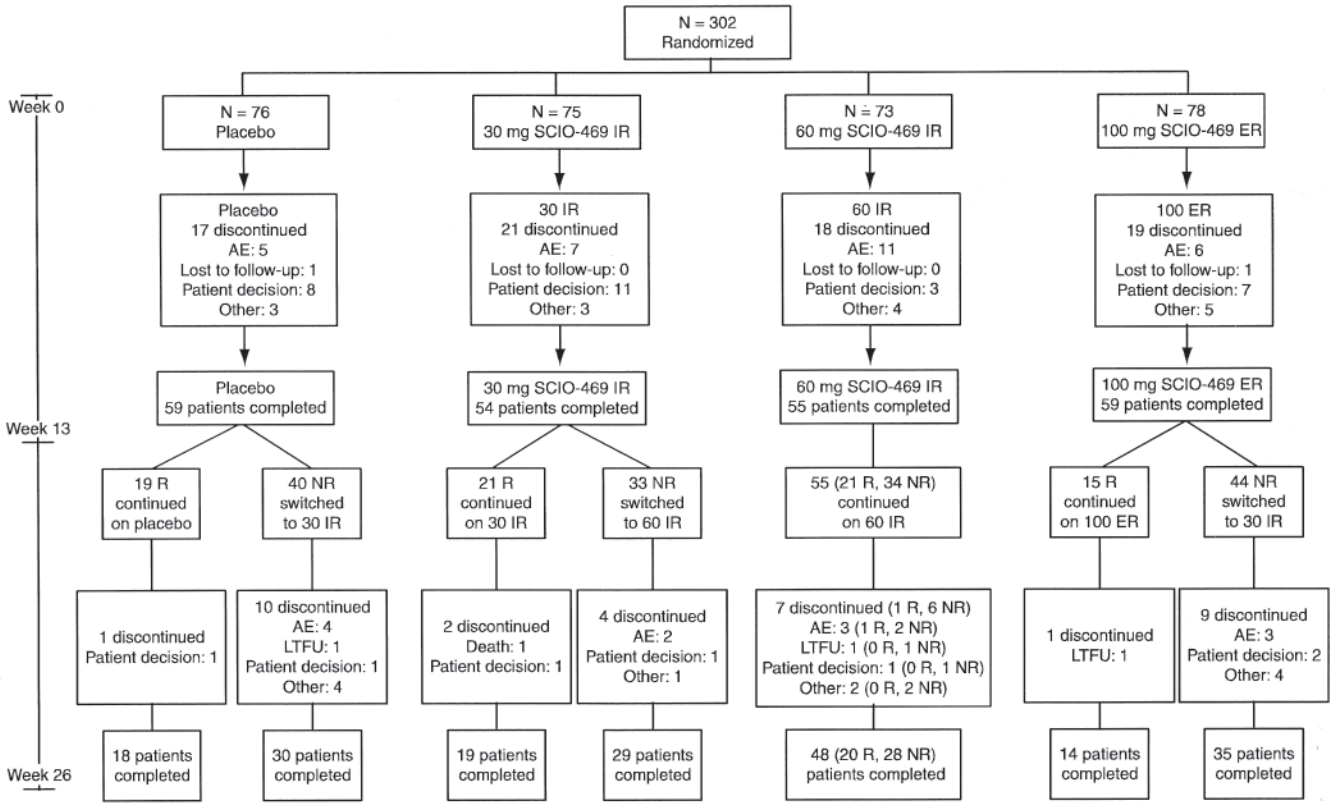

Figure 1. Patient disposition. IR: immediate release; ER: extended release; AE: adverse event; LTFU: lost to followup; NR: nonresponder; R: responder.

similar among the treatment groups. One hundred twenty-eight patients (43%) were methotrexate-naive at baseline.

Nearly all patients (298/301; 99%) received concomitant medications through Week 12, with 76% taking COX-2 inhibitors and NSAID and 8.0% receiving 1 of the 4 allowed DMARD during the study. Concomitant medication use remained consistent after Week 12, and there were no sig-

Table 1. Baseline demographics and disease characteristics. Data presented as n (%) unless otherwise noted.

Characteristics	Placebo, n = 76	30 mg IR, n = 74	60 mg IR, n = 73	100 mg ER, n = 78	All Patients, n = 301
Age, yrs, mean (SD)	55.1 (12.20)	55.1 (13.41)	54.7 (13.73)	52.4 (12.16)	54.3 (12.86)
Women	59 (77.6)	59 (79.7)	60 (82.2)	64 (82.1)	242 (80.4)
Race					
White	62 (81.6)	58 (78.4)	58 (79.5)	57 (73.1)	235 (78.1)
Black	10 (13.2)	13 (17.6)	10 (13.7)	9 (11.5)	42 (14.0)
Hispanic	2 (2.6)	2 (2.7)	3 (4.1)	12 (15.4)	19 (6.3)
Weight, kg, mean (SD)	82.3 (19.18)	85.0 (20.95)	82.7 (18.20)	79.5 (19.37)	82.3 (19.46)
ACR classification of RA					
II	40 (52.6)	46 (62.2)	44 (60.3)	36 (46.2)	166 (55.1)
III	27 (35.5)	23 (31.1)	25 (34.2)	30 (38.5)	105 (34.9)
Disease duration, yrs, mean SD	7.5 (7.96)	7.1 (8.05)	10.7 (10.34)	9.1 (9.21)	8.6 (9.01)
C-reactive protein, mg/dl, mean (SD)	2.14 (3.595)	1.82 (2.804)	1.44 (1.802)	1.66 (2.428)	1.77 (2.739)
Patients with CRP < 1 mg/dl	44 (57.9)	43 (58.1)	51 (69.9)	51 (65.4)	189 (62.8)
DAS 28					
≤ 3.2	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.7)
> 3.2 to ≤ 5.1	21 (27.6)	32 (43.2)	27 (37.0)	28 (35.9)	108 (35.9)
> 5.1	54 (71.1)	42 (56.8)	46 (63.0)	49 (62.8)	191 (63.5)

ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28: Disease Activity Score using 28 joint counts; ER: extended release; IR: immediate release; RA: rheumatoid arthritis.

nificant differences in medication use between responders and nonresponders (data not shown).

Efficacy. All patients who received ≥ 1 dose of study agent (placebo or SCIO-469) with at least 1 evaluable followup visit were included in the efficacy analysis (n = 299). At Week 12, there were no significant differences in the primary endpoint of the proportions of ACR20 responders in SCIO-469 groups (30 mg IR, 26%; 60 mg IR, 33%; 100 mg ER, 23%) compared with placebo (24%; Table 2). ACR20 response rates were greater in the 30 mg IR and 60 mg IR groups compared with placebo at all other time points through Week 13, with the greatest difference observed from Weeks 2 to 8 and attenuated by Week 13; the 100 mg ER group did not show higher response rates than placebo past Week 4 (Figure 2A). There were no differences in ACR50 response between any active group and placebo through Week 13 (data not shown). After Week 13, a total of 227 patients continued in the study and either received their original assigned treatment or were re-randomized to an alternative treatment (Figure 1).

There were no significant differences between active treatment groups and placebo in secondary efficacy endpoints, including mean changes in the swollen and tender joint counts, physician global assessment, and DAS28 response (data not shown). For patient global assessment, the 30 mg IR and 60 mg IR treatment groups displayed a clear tendency toward greater improvement at all time points during the first 12 weeks of treatment, although results for the 100 mg ER treatment group were similar to placebo (Figure 2B). All 3 SCIO-469 groups reported improvements in median percent changes from baseline in the VAS assessment of pain up to Week 4 when compared with placebo (Figure 2C); however, no significant differences were observed between active treatment groups and placebo from Weeks 6 through 12. Mean improvements in HAQ scores were reported in the 30 and 60 mg IR groups baseline to Week 12 when compared with placebo (Figure 2D), and exceeded minimum clinically meaningful improvements of ≥ 0.22 in the 60 mg IR group at all time points, Weeks 6 through 12. At early timepoints, especially at Week 1, significant decreases in median percent changes from baseline in CRP (Figure 2E) and ESR (Figure 2F) levels were evident in all 3 SCIO-469 groups; however, these differences were no longer evident after Week 4.

Serum samples from the first 120 patients enrolled who had a baseline CRP of 0.8 mg/dl or higher, a total of 106 patients, were included in a biomarker analysis of IL-6, IL-1R-α (as a surrogate for IL-1ß), IL-8, ICAM-1, and MMP-3. No physiologically important changes from baseline were noted in any treatment group for any of the biomarkers studied (data not shown).

Rheumatoid factor data were collected as part of the diagnosis for RA, while anticyclic citrullinated peptide (anti-CCP) data were collected only at baseline. There were 51% anti-CCP-positive patients and 45% anti-CCP-negative patients. An ad hoc analysis showed that patients treated with SCIO-469 with baseline negative anti-CCP values had a higher ACR20 response rate (37%) than treated patients with positive baseline anti-CCP values (19%); statistical analyses were not performed.

Safety. Among all patients, 240 (80%) reported at least 1 AE during the initial 13 weeks of treatment, with greater proportions of patients in 30 mg IR and 60 mg IR groups experiencing AE compared with 100 mg ER and placebo groups (Table 3). Through 26 weeks, 261 patients (87%) reported at least 1 AE; with the highest proportion in those receiving 60 mg IR. A summary of AE reported by at least 5% of all patients is shown in Table 3. Upper respiratory tract infection was the most commonly reported AE and occurred most frequently in placebo and 60 mg IR groups. Arthralgia, constipation, rash, and dizziness were reported more often by patients who received SCIO-469 than by those who received placebo. Eleven patients had levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal (ULN) during the 24-week treatment period; 8 of these elevations were reported as AE (in 1 placebo-treated patient, 1 placebo-switched to 30-mg patient, 1 30-mg-treated patient, and five 60-mg-treated patients). Among these patients, ALT levels ranged up to 44 times ULN in 1 60-mg-treated patient. These elevations were transient and not associated with bilirubin values ≥ 2 times ULN.

Because of the prior incidence of rash in patients who received SCIO-469 in previous trials, study sites were instructed to record additional information about the follow-

Table 2. Proportion of patients who achieved ACR20 or ACR50 responses at Week 12.

	Placebo, n = 75	30 mg IR n = 73	60 mg IR, n = 73	100 mg ER, n = 78	Combined, n = 224
ACR20, n (%)	18 (24.0)	19 (26.0)	24 (32.9)	18 (23.1)	61 (27.2)
p	—	0.780	0.222	0.897	0.583
ACR50, n (%)	7 (9.3)	6 (8.2)	12 (16.4)	6 (7.7)	24 (10.7)
p	—	0.824	0.156	0.739	0.734

ACR20: 20% improvement in American College of Rheumatology criteria; ACR50: 50% improvement in ACR criteria.

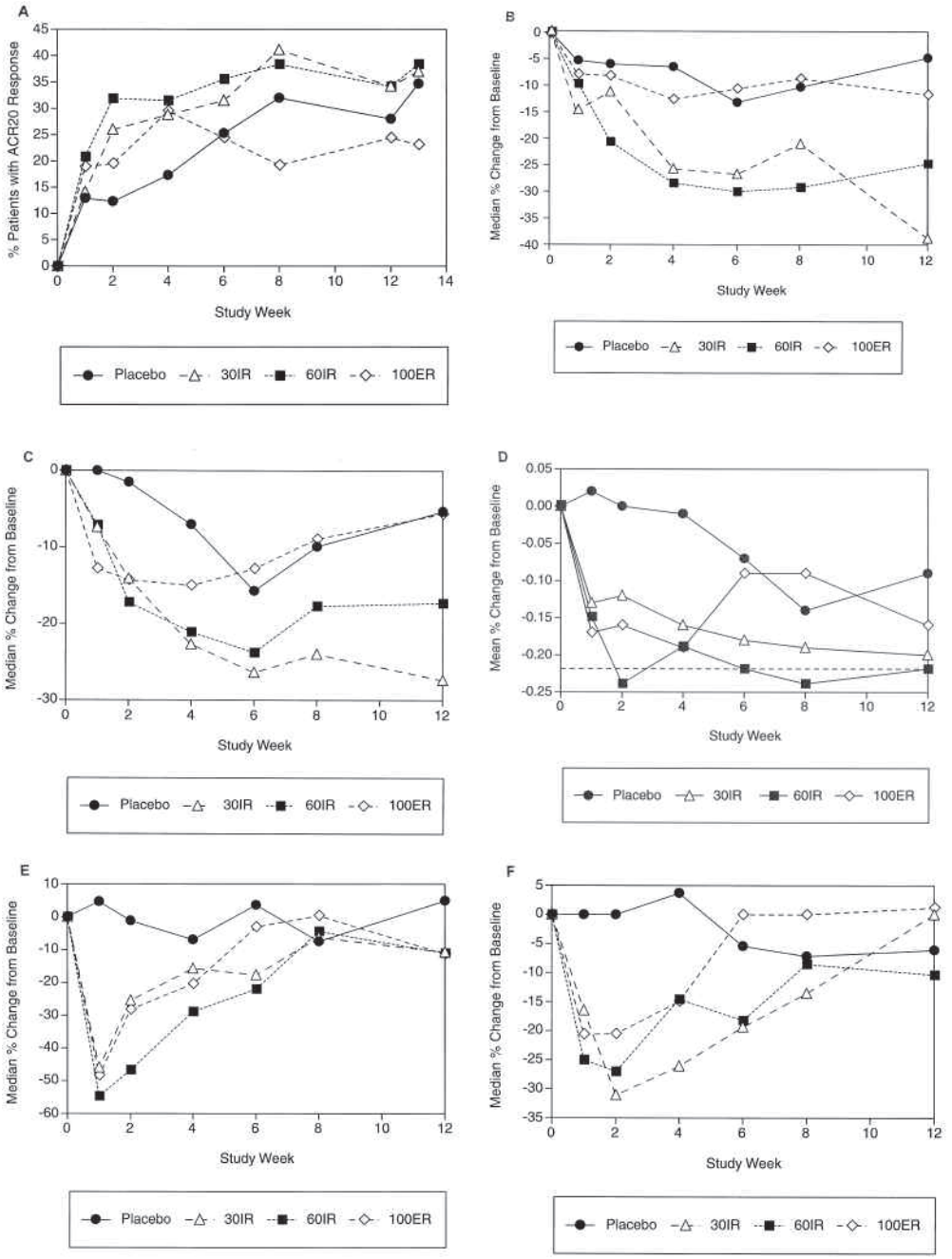

Figure 2. (A) American College of Rheumatology 20 response through Week 13. Median percent change from baseline to Week 12 in (B) patient's global assessment, and (C) pain visual analog scale. (D) Mean percent change from baseline to Week 12 in Health Assessment Questionnaire. The dotted line represents clinically meaningful change. Median percent change from baseline to Week 12 in (E) C-reactive protein and (F) erythrocyte sedimentation rate. IR: immediate release; ER: extended release.

ing AE: rash, erythematous rash, maculopapular rash, generalized rash, acne, dermatitis acneiform, allergic dermatitis, and erythema. This information was further reviewed and categorized by a dermatologist as localized or generalized rash or acne. The occurrence of rash in this study appeared to be dose-dependent, with the highest incidence in the 60 mg IR group (Table 3). However, no dose-dependent relationship was apparent between SCIO-469 treatment and type of rash.

Serious AE (SAE) were reported by 11 patients during the initial 13 weeks of treatment and by 21 patients through 26 weeks (Table 4). No SAE occurred in the SCIO-469 100 mg ER group. Infections/infestations, gastrointestinal disorders (excluding elevated liver enzymes), and cardiac dis-

Table 3. Common adverse events (AE) reported in ≥ 5% of all patients and AE of interest. Data reported as n (%).

	Placebo	30 mg IR	60 mg IR	100 mg ER	All Patients
During the initial 13 weeks of the study	n = 76	n = 74	n = 73	n = 78	n = 301
Patients with AE	57 (75.0)	63 (85.1)	60 (82.2)	60 (76.9)	240 (79.7)
Common AE					
Upper respiratory tract infection	20 (26.3)	6 (8.1)	17 (23.3)	7 (9.0)	50 (16.6)
Nausea	6 (7.9)	3 (4.1)	7 (9.6)	7 (9.0)	23 (7.6)
Rheumatoid arthritis*	1 (1.3)	9 (12.2)	4 (5.5)	9 (11.5)	23 (7.6)
Urinary tract infection	4 (5.3)	6 (8.1)	3 (4.1)	5 (6.4)	18 (6.0)
Rash	2 (2.6)	7 (9.5)	4 (5.5)	4 (5.1)	17 (5.6)
Arthralgia	0	6 (8.1)	4 (5.5)	6 (7.7)	16 (5.3)
Diarrhea	5 (6.6)	4 (5.4)	4 (5.5)	3 (3.8)	16 (5.3)
Dizziness	2 (2.6)	3 (4.1)	4 (5.5)	7 (9.0)	16 (5.3)
Patients with any rash	3 (3.9)	10 (13.5)	13 (17.8)	8 (10.3)	34 (11.3)
Localized	2 (2.6)	5 (6.8)	4 (5.5)	2 (2.6)	13 (4.3)
Acne	0	3 (4.1)	5 (6.8)	2 (2.6)	10 (3.3)
Generalized	1 (1.3)	2 (2.7)	5 (6.8)	2 (2.6)	10 (3.3)
No information available	0	0	0	2 (2.6)	2 (0.7)
During 26 weeks (including data during initial 13 weeks)	n = 76	n = 158†	n = 106†	n = 78	n = 301
Patients with AE	59 (77.6)	126 (79.7)	93 (87.7)	61 (78.2)	261 (86.7)
Common AE					
Upper respiratory tract infection	22 (28.9)	12 (7.6)	25 (23.6)	10 (12.8)	67 (22.3)
Rheumatoid arthritis*	6 (7.9)	25 (15.8)	17 (16.0)	13 (16.7)	57 (18.9)
Nausea	7 (9.2)	7 (4.4)	14 (13.2)	7 (9.0)	34 (11.3)
Urinary tract infection	5 (6.6)	14 (8.9)	9 (8.5)	6 (7.7)	29 (9.6)
Rash	2 (2.6)	11 (7.0)	9 (8.5)	5 (6.4)	26 (8.6)
Arthralgia	1 (1.3)	10 (6.3)	9 (8.5)	7 (9.0)	26 (8.6)
Dizziness	2 (2.6)	8 (5.1)	7 (6.6)	7 (9.0)	23 (7.6)
ALT increased	3 (3.9)	6 (3.8)	12 (11.3)	2 (2.6)	21 (7.0)
Sinusitis	4 (5.3)	8 (5.1)	5 (4.7)	5 (6.4)	21 (7.0)
Diarrhea	5 (6.6)	5 (3.2)	7 (6.6)	3 (3.8)	20 (6.6)
Bronchitis	4 (5.3)	6 (3.8)	4 (3.8)	3 (3.8)	17 (5.6)
AST increased	2 (2.6)	6 (3.8)	11 (10.4)	0	17 (5.6)
Cough	2 (2.6)	4 (2.5)	6 (5.7)	3 (3.8)	15 (5.0)
Patients with any rash	3 (3.9)	16 (10.1)	19 (17.9)	9 (11.5)	46 (15.3)
Localized	2 (2.6)	6 (3.8)	6 (5.7)	2 (2.6)	16 (5.3)
Acne	0	5 (3.2)	6 (5.7)	3 (3.8)	14 (4.7)
Generalized	1 (1.3)	5 (3.2)	6 (5.7)	2 (2.6)	14 (4.7)
No information available	0	0	2 (1.8)	2 (2.6)	4 (1.3)

*Worsening of baseline disease. †Includes patients originally assigned to these groups as well as those who were rerandomized to receive these treatments at Week 13. IR: immediate release; ER: extended release; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

orders were the most common SAE. Infections/infestations and gastrointestinal disorder SAE occurred only in patients who received SCIO-469, while cardiac disorders occurred in placebo and 30 mg IR groups. Through 26 weeks, 46 patients (15%) discontinued treatment because of an AE. The most common reasons for treatment discontinuations were elevations in levels of ALT (n = 6) and/or AST (n = 5). Two deaths were reported during the trial: 1 due to murder in the placebo group (the patient had withdrawn from the study because of an AE the day before death), and the other due to pulmonary fibrosis and respiratory failure in the 30 mg IR group. Neither death was attributed to the study drug.

Pharmacokinetics. Plasma trough SCIO-469 concentrations from all treatment groups reached steady state by the first posttreatment pharmacokinetic assessment at Week 1. Mean plasma trough concentrations from all time points through Week 12 in the 60 mg IR group (399.3 ng/ml) were about twice those of the 30 mg IR group (199.5 ng/ml), and mean trough concentrations were comparable between the 30 mg IR and 100 mg ER groups (199.5 ng/ml vs 196.8 ng/ml). No evidence of saturable metabolism and enzyme induction was observed based on the average trough concentration-time data. By visual inspection, comparisons of concentration-time profiles for the 2 primary metabolites, M1 and M2, were similar for all 3 SCIO-469 treatment regimens.

An ad hoc analysis demonstrated no statistically significant differences in SCIO-469 average plasma trough concentrations in patients with or without ACR20 response at Week 12, no differences in patients with or without occurrence of rash, and no correlation with change in CRP values at Week 1, suggesting no dose-response relationship in the dose regimens studied (data not shown).

Table 4. Serious adverse events (SAE). Data reported as n (%).

	Placebo	30 mg IR	60 mg IR	100 mg ER	All Patients
During the initial 13 weeks of the study	n = 76	n = 74	n = 73	n = 78	n = 301
Patients with SAE	3 (3.9)	4 (5.4)	4 (5.5)	0	11 (3.7)
Colitis	0	1 (1.4)	0	0	1 (0.3)
Colitis ischemic	0	1 (1.4)	0	0	1 (0.3)
Duodenal ulcer	0	0	1 (1.4)	0	1 (0.3)
Cellulitis	0	0	1 (1.4)	0	1 (0.3)
ALT increased	0	1 (1.4)	0	0	1 (0.3)
AST increased	0	1 (1.4)	0	0	1 (0.3)
Drug withdrawal	1 (1.3)	0	0	0	1 (0.3)
Generalized edema	0	0	1 (1.4)	0	1 (0.3)
Asthma	0	1 (1.4)	0	0	1 (0.3)
Hyperglycemia	0	0	1 (1.4)	0	1 (0.3)
Atrial fibrillation	0	1 (1.4)	0	0	1 (0.3)
Congestive cardiac failure	1 (1.3)	0	0	0	1 (0.3)
During 26 weeks (including data during initial 13 weeks)	n = 76	n = 158*	n = 106*	n = 78	n = 301
Patients with SAE	3 (3.9)	10 (6.3)	8 (7.5)	0	21 (7.0)
Cellulitis	0	0	2 (1.9)	0	2 (0.7)
Pneumonia	0	1 (0.6)	1 (0.9)	0	2 (0.7)
Clostridial infection	0	0	1 (0.9)	0	1 (0.3)
Diverticulitis	0	1 (0.6)	0	0	1 (0.3)
Gastroenteritis viral	0	0	1 (0.9)	0	1 (0.3)
Localized infection	0	0	1 (0.9)	0	1 (0.3)
Atrial fibrillation	0	1 (0.6)	0	0	1 (0.3)
Congestive cardiac failure	1 (1.3)	1 (0.6)	0	0	2 (0.7)
Myocardial infarction	0	1 (0.6)	0	0	1 (0.3)
Colitis	0	1 (0.6)	0	0	1 (0.3)
Colitis ischemic	0	1 (0.6)	0	0	1 (0.3)
Duodenal ulcer	0	1 (0.6)	1 (0.9)	0	2 (0.7)
Drug withdrawal syndrome	1 (1.3)	0	0	0	1 (0.3)
Generalized edema	0	0	1 (0.9)	0	1 (0.3)
Asthma	0	1 (0.6)	0	0	1 (0.3)
Respiratory failure	0	1 (0.6)	0	0	1 (0.3)
Hyperglycemia	0	0	1 (0.9)	0	1 (0.3)
ALT increased	0	1 (0.6)	0	0	1 (0.3)
AST increased	0	1 (0.6)	0	0	1 (0.3)
Acute myeloid leukemia	0	1 (0.6)	0	0	1 (0.3)
Syncope	0	1 (0.6)	0	0	1 (0.3)
Deep vein thrombosis	0	1 (0.6)	0	0	1 (0.3)

*Includes patients originally assigned to these groups as well as those who were re-randomized to receive these treatments at Week 13. IR: immediate release; ER: extended release; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

DISCUSSION

This study evaluated the efficacy, safety, and tolerability of 2 IR and 1 ER doses of the p38 MAPK inhibitor SCIO-469 in patients with active RA not taking background DMARD with the exception of stable-dose hydroxychloroquine, chloroquine, minocycline, and doxycycline. There were no meaningful differences in efficacy seen between any active treatment arm and placebo. Impressive decreases in acute-phase reactants CRP and ESR were initially seen by Week 2 after randomization; however, these returned to near baseline values by Weeks 8 to 12. Minor improvements were evident in other components of the ACR responder criteria and DAS; however, no significant separation was seen between active treatment and placebo.

Pharmacokinetic studies demonstrated that steady state was achieved with active therapy by Week 1 and remained stable throughout the study. Thus, the observed changes in acute-phase reactants were not related to changes in the pharmacokinetic assessment of the study drug or its metabolites. In addition, efficacy responses did not appear to correlate with steady state concentrations achieved following administration of either IR or ER formulations. AE were reported similarly in all treatment arms, with the exception of higher numbers of rashes and liver function elevations in the 60 mg IR dose. SAE were more common in the IR active treatment arms than in the placebo arm, and were not reported in the ER active arm.

Despite the much-heralded development history of p38 MAPK inhibitors, there is little evidence that this is an effective approach to the treatment of RA. A previous edito-

rial and more recent publications have now begun to provide insight into the use of this targeted approach in RA and the spondyloarthropathies[14,15,16,17,18].

Cohen, *et al* reported on the development of a p38 MAPK inhibitor, pamapimod (RO4402257), a selective inhibitor of the α-isoform of p38[14], in the first full-length article published on the use of a p38 inhibitor for the treatment of RA. Pamapimod was studied as a monotherapy and compared with methotrexate in patients with active RA. Despite 12 weeks of daily therapy with one of 3 doses of pamapimod (50, 150, or 300 mg), no clear evidence of efficacy was observed. Overall, AE, including infections, skin disorders, dizziness, and elevated liver enzymes, were more frequent in the pamapimod treatment groups than in the methotrexate treatment group. Damjanov, *et al* subsequently published the results of 2 separate studies of VX-702 in patients with RA with and without background methotrexate[15]. In both studies, no meaningful benefit was demonstrated as compared with the control groups. Finally, a study of ARRY-797 in ankylosing spondylitis[17] was unable to demonstrate benefits in comparison with the control group.

Contemporaneously with these studies, SCIO-469, one of the first selective p38-α inhibitors to be studied for the treatment of RA, entered clinical trials. The early evidence of potential benefit in animal models led us to pursue human investigation and ultimately to proceed with this phase II trial. Because of the perceived association between transaminase elevations and p38 MAPK inhibitors, we designed this study as a monotherapy trial and did not permit methotrexate as a background therapy. Despite this attempt to reduce this potential adverse effect, elevated ALT levels were still seen more frequently in the 60 mg IR dose group.

Perhaps the most intriguing result of this trial and the other p38 MAPK trials is that of the posttreatment trend seen in CRP and ESR. The initial decline in these acute-phase reactants was followed by a rapid return to baseline over a period of several weeks. This finding is not an isolated event seen in 1 study, but rather a finding that has been demonstrated repeatedly with this class of therapeutic agents across various diseases[19]. The etiology of this phenomenon remains unknown but presumably lies in 1 or more biologic adaptations that allow escape from the p38 MAPK pathway, such as the upregulation of enzymes proximal or distal to p38 MAPK in this pathway or the upregulation of 1 or more unidentified factors in another inflammatory pathway. For example, p38 MAPK regulates certain antiinflammatory cytokines such as IL-10, which might offset the benefit of TNF and IL-6 inhibition in RA[20]. Alternatively, relative lack of central nervous system penetration could limit the analgesic and antiinflammatory effects of p38 MAPK inhibitors[21]. Escape mechanisms that shunt the signaling flux to other proinflammatory pathways, such as nuclear factor-κB, could contribute to an adaptive response that limits the decrease in acute-phase reactants despite adequate drug levels. Recent successes with other kinase inhibitors in RA, such as with the Syk family of tyrosine kinase proteins and Janus kinase blockade[22,23], suggest that blocking signaling at a more proximal step than p38 MAPK itself might overcome some of these obstacles.

Treatment with SCIO-469 failed to demonstrate meaningful clinical benefit in patients with RA in this trial. Similar to the fate of many other agents targeting p38 MAPK, SCIO-469 is no longer in clinical development. It has now become clearer that there are class-related issues with the efficacy of p38 MAPK inhibition in RA. The reason for only transient benefits with p38 MAPK inhibitors remains unknown.

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