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ORIGINAL RESEARCH

Repository Corticotropin Injection for Active Rheumatoid Arthritis Despite Aggressive Treatment: A Randomized Controlled Withdrawal Trial

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ABSTRACT

Introduction: The objective of this study was to assess efficacy and safety of repository corticotropin injection (RCI) in subjects with active rheumatoid arthritis (RA) despite treatment with a corticosteroid and one or two disease-modifying antirheumatic drugs (DMARDs).

Methods: All subjects received open-label RCI (80 U) twice weekly for 12 weeks (part 1); only those with low disease activity [LDA; i.e., Disease Activity Score 28 joint count and erythrocyte sedimentation rate (DAS28-ESR) < 3.2] were randomly assigned to receive either RCI (80 U) or placebo twice weekly during the 12-week double-blind period (part 2). The primary efficacy endpoint was the proportion of subjects who achieved LDA at week 12. Secondary efficacy endpoints included proportions of subjects who maintained LDA during weeks 12 through 24 and achieved Clinical Disease Activity Index (CDAI) ≤ 10 at weeks 12 and 24. Safety was assessed via adverse event reports.

Results: Of the 259 enrolled subjects, 235 completed part 1; 154 subjects ($n = 77$ each for RCI and placebo) entered part 2, and 127 (RCI, $n = 71$; placebo, $n = 56$) completed. At week 12, 163 subjects (62.9%) achieved LDA and 169 (65.3%) achieved CDAI ≤ 10 (both $p < 0.0001$). At week 24, 47 (61.0%) RCI-treated and 32 (42.1%) placebo-treated subjects maintained LDA ($p = 0.019$); 66 (85.7%) RCI-treated and 50 (65.8%) placebo-treated subjects maintained CDAI ≤ 10 ($p = 0.004$). No unexpected safety signals were observed.

Conclusions: RCI was effective and generally safe in patients with active RA despite corticosteroid/DMARD therapy. By week 12, $> 60\%$ of patients achieved LDA, which was maintained with 12 additional weeks of treatment. Most

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patients who achieved LDA maintained it for 3 months after RCI discontinuation.
Trial Registration: Clinicaltrials.gov identifier NCT02919761.

Keywords: Active disease; Clinical trial; Corticosteroids; Disease-modifying antirheumatic drugs; Low disease activity; Repository corticotropin injection; Rheumatoid arthritis; Withdrawal study

Key Summary Points

Why carry out this study?

Despite the availability of numerous biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) and despite using glucocorticoids, many patients with rheumatoid arthritis (RA) are unable to achieve or maintain remission or low disease activity (LDA) with these agents and, as a result, may sustain irreversible joint damage.

Repository corticotropin injection (RCI) is a naturally sourced complex mixture of adrenocorticotropic hormone analogues and other pituitary peptides that functions as an agonist of all five melanocortin receptors and has several potential mechanistic pathways that may contribute to its therapeutic effects in RA.

The current study was undertaken to confirm findings from previous small open-label studies by assessing the efficacy, safety, and tolerability of RCI in a larger population of subjects with active RA despite treatment with prednisone (or an equivalent) and one or two conventional synthetic DMARDs or one biologic DMARD via a randomized, double-blind, placebo-controlled withdrawal trial with an open-label run-in period.

What was learned from this study?

> 60% of patients achieved LDA during 12 weeks of open-label RCI therapy, which was maintained with 12 additional weeks of RCI maintenance therapy; most patients who achieved LDA maintained it for 3 months after RCI discontinuation.

In patients with active RA despite corticosteroid/DMARD therapy, RCI was generally safe and was associated with significant, durable, and beneficial effects on disease activity.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease in which proinflammatory cytokines act as mediators of synovial inflammation, with resulting bone and cartilage damage in multiple joints [1, 2]. Although the distribution of RA varies by age and geographic location, in developed countries the estimated incidence and prevalence of RA in adults range from 5 to 50 per 100,000 and 0.5–1.0%, respectively [3]. A treat-to-target approach has been advocated for RA, with the goal being remission or low disease activity (LDA) if remission cannot be obtained [4, 5]. The cornerstones for treatment are conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs, which suppress inflammation that leads to eventual joint damage [6]. If instituted early, effective DMARD therapy may prevent irreversible joint damage and improve function [6].

Rates of remission and clinical response in DMARD-treated patients with RA vary widely depending on the agents used, whether monotherapy or combination therapy is employed, the time point(s) assessed, and the criteria for defining *remission* and *response*—whether strict, such as the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) definitions [4, 5], or less stringent, such as Disease Activity Score

with 28 joint count and erythrocyte sedimentation rate (DAS28-ESR) < 2.6. Generally, at 1 year, estimates of remission range from 25% with strict metrics to 55% with less stringent metrics, and response rates to therapy range from 35–65% [7]. Thus, despite availability of numerous biologic and nonbiologic DMARDs, substantial proportions of patients are unable to achieve or maintain remission or LDA with these agents and may sustain irreversible joint damage and associated decline in their ability to perform basic physical activity [6].

Corticosteroids are often used to rapidly control inflammation in patients with RA who are initiating or changing DMARD therapy, but their association with numerous adverse events (AEs) limits their use [4, 5, 8]. Of particular concern in patients with RA, corticosteroid use for > 3 months, particularly at a high dose, is associated with rapid, persistent bone loss, which contributes to increased risk of osteoporosis and fractures [1]. Hence, additional treatment options for patients with RA are needed.

Repository corticotropin injection (RCI; Acthar® Gel) is a naturally sourced complex mixture of adrenocorticotropic hormone analogues and other pituitary peptides. As an agonist of all five melanocortin receptors (MCRs), RCI has several potential mechanistic pathways that may contribute to its therapeutic effects in RA [9, 10]. Results from preclinical studies suggest several nonsteroidogenic pathways for RCI that may affect inflammation and immune regulation. Activation of MCR1 has been shown to affect the nuclear factor-κB (NF-κB) pathway, leading to downregulation of inflammatory cytokines [11–13]. Multiple cells of the immune system express MCR1, MCR3, and/or MCR5, suggesting they have additional roles in mediating inflammation [11, 14, 15]. Further, MCR1 and MCR5 are present on human articular chondrocytes and rheumatoid synovial fibroblasts, which are involved in the chronic immune response in RA [11, 16]. All five MCRs are expressed on osteoclasts and osteoblasts [17, 18], a finding that could have implications for the bone resorption associated with RA [11, 14, 15, 18].

The evidence for the clinical effectiveness of RCI in patients with RA was suggested in small open-label studies [19–21]. The current study was undertaken to confirm these findings in a larger population via a randomized, double-blind, placebo-controlled withdrawal trial with an open-label run-in period. Our objective was to assess the efficacy, safety, and tolerability of RCI in subjects with active RA despite treatment with prednisone (or an equivalent) and one or two csDMARDs or one bDMARD.

METHODS

Study Design

The design of this two-part multicenter, randomized, placebo-controlled withdrawal study is shown in Fig. 1. All enrolled subjects received open-label RCI (1 ml, 80 U) subcutaneously twice weekly for 12 weeks (part 1), a dosage that previous studies suggest is effective [20, 21]. Subjects were then assessed for treatment response using the DAS28-ESR, with thresholds of 2.6, 3.2, and 5.1 suggesting remission, LDA, and high disease activity, respectively [22, 23]. Subjects who achieved LDA (DAS28-ESR < 3.2) at week 12 were randomly assigned to receive either subcutaneous RCI (1 ml, 80 U) or matching placebo (1 ml) twice weekly during the 12-week, double-blind withdrawal period (part 2).

The study was conducted at 60 centers in four countries (see electronic supplementary material for details on study centers) from November 7, 2016, to February 13, 2019, in accordance with the principles and requirements of the Declaration of Helsinki, Good Clinical Practices, and clinical trial registration (clinicaltrials.gov identifier NCT02919761). All investigators obtained institutional review board/independent ethics committee approval. All subjects provided informed consent (including consent for publication) before any study procedures were performed.

Key Study Entry Criteria

Individuals eligible for participation included men and nonpregnant, nonlactating women aged ≥ 18 years who met the 2010 ACR/EULAR criteria [24] for having RA that was active,

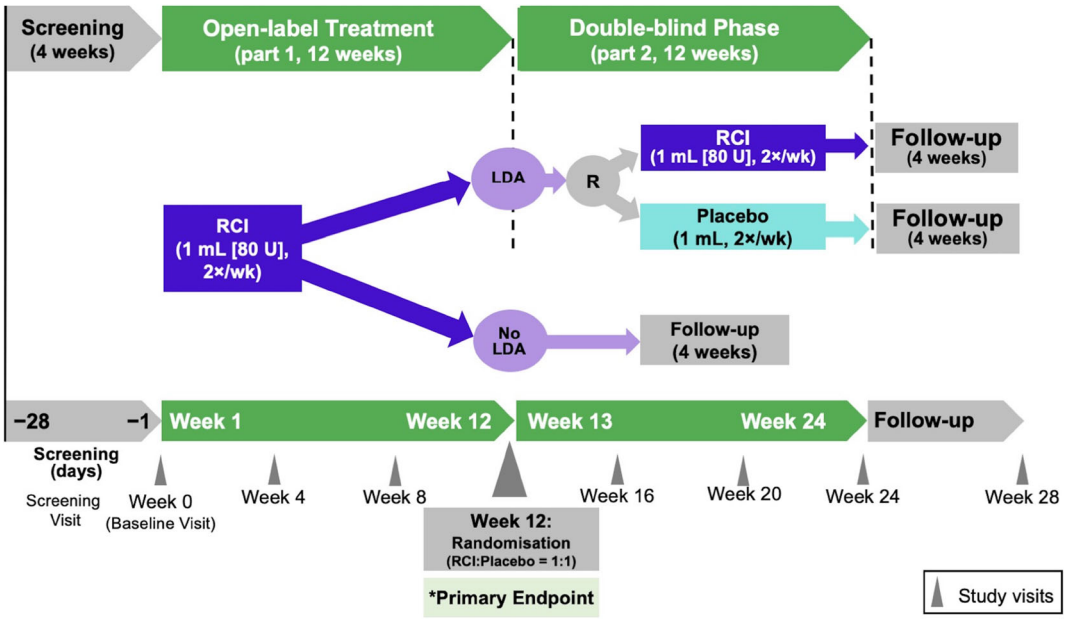

Fig. 1 Study design. *LDA* low disease activity, *R* randomization, *RCI* repository corticotropin injection

defined as DAS28-ESR > 3.2, despite treatment with a stable dose (5–10 mg) of prednisone (or equivalent) and one or two csDMARDs or one bDMARD (Table S1 in the electronic supplementary material). Subjects who were taking nonsteroidal anti-inflammatory drugs were required to be on a stable dose for 4 weeks before screening and remain on a stable dose throughout study participation.

Individuals were ineligible for participation if they had any rheumatic autoimmune disease or inflammatory joint disease other than RA, had a history of using adrenocorticotropic hormone (ACTH) preparations for RA or a history of sensitivity to ACTH preparations, or had known contraindications to RCI use; had used any investigational treatment for RA or any biologic investigational agent in the 24 weeks before the first dose of study drug, any non-biologic investigational agent within 6 weeks before the first dose of study drug, B cell-mediated therapies in the 24 weeks before screening, or intraarticular corticosteroids within 14 days before screening; or had type 1 or type 2 diabetes mellitus, a history of chronic active hepatitis or tuberculosis, a solid tumor or hematologic malignancy, drug/alcohol abuse, or a clinically significant infection.

The use of intraarticular steroids; live or attenuated vaccines; enteral or parenteral immunosuppressive medications; or an investigational drug, device, or procedure administered as part of a research study was not permitted during the trial.

Procedures and Interventions

Within 28 days after screening, enrolled subjects underwent baseline evaluations, which included calculation of their DAS28-ESR. At the baseline visit, all subjects received their first dose of open-label RCI (1 ml, 80 U) and were observed for 1 h afterward. Subsequent open-label RCI doses were administered twice weekly at home by the subject or caregiver. Subjects returned to the study center at weeks 4, 8, and 12 (part 1) for efficacy and safety assessments. At week 12, subjects who had achieved LDA (DAS28-ESR < 3.2) were randomly assigned (in a 1:1 ratio) to receive either 1 ml (80 U) of RCI or 1 ml of placebo subcutaneously twice weekly during the 12-week double-blind period (part 2), which was designed to evaluate maintenance of response to therapy. Subjects who did not achieve LDA at week 12 were discontinued from further study participation.

During the double-blind period, subjects returned to the study center at weeks 16 and 24 for efficacy and safety assessments. Blood and urine samples for analysis of bone turnover markers were collected at weeks 12 and 24. At the follow-up visit, 28 days after the final dose of study drug, safety assessments were completed.

Bone turnover markers were analyzed by Eurofins Central Laboratory (Breda, The Netherlands). C-terminal crosslinking telopeptide (CTX), CTX-I, and N-terminal propeptide of type I collagen (PINP) were evaluated via electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA); enzyme-linked immunosorbent assay was used to assess CTX-II (Immunodiagnostic Systems, East Boldon, UK), osteoprotegerin (OPG; Quidel, San Diego, CA, USA), and soluble receptor activator of NF-κB ligand (sRANKL; BioVendor, Karasek, Czech Republic). Creatinine was evaluated via Jaffe reaction using alkaline picrate (Roche Diagnostics, Indianapolis, IN, USA), and creatinine-adjusted CTX-II (CTX-II CRT) was calculated using the following formula:

$$\text{CTX-II CRT (ng/mmol)} = 1000 \times \text{CTX-II (}\mu\text{g/L)/creatine (mmol/L)}.$$

Randomization and Blinding

Almac Clinical Technologies generated the randomization sequence, which used a block size of 4 and a 1:1 treatment allocation ratio. Four hundred randomization numbers (200 per treatment group) were generated, and randomization activities were conducted via the IXRS (interactive phone/web response system). A dummy subject randomization list was used for IXRS development and for Almac/client user acceptance testing. Except for those who prepared the randomization protocol and those involved in study drug preparation, all parties were blinded to subjects' treatment conditions during the double-blind period.

Endpoints

The primary efficacy endpoint was the proportion of subjects who achieved DAS28-ESR < 3.2 at week 12 in part 1 of the study. Secondary efficacy endpoints included the proportion of subjects who maintained DAS28-ESR < 3.2 from week 12 through week 24; time to disease activity flare (as defined below) from weeks 12 through 24; the proportion of subjects with Clinical Disease Activity Index (CDAI) LDA (i.e., CDAI ≤ 10) [25] at weeks 12 and 24; and the proportion of subjects who met ACR criteria for 20% improvement (ACR20) at weeks 12 and 24. For weeks 13 through 23, *disease activity flare* was defined as meeting one of the following criteria: (1) DAS28-ESR < 3.2 and an increase of 1.2 from week 12; (2) DAS28-ESR ≥ 3.2 and an increase of > 0.6 from the week 12 assessment sustained over two consecutive visits; or (3) DAS28-ESR ≥ 3.2 and an increase of > 1 from the week 12 assessment at a single visit. Criteria 1 and 2 were based on validated criteria for RA flares [26, 27]; the third criterion was developed on the basis of the first two criteria, with slight modification for more stringency to capture potential flares not meeting criterion 1 or 2.

Exploratory endpoints included the proportions of subjects who achieved ACR50 and ACR70 responses at weeks 12 and 24 (with week 24 evaluated post hoc); the proportion of subjects with DAS28-ESR < 2.6 at weeks 12 and 24; and changes from baseline to weeks 12 and 24 in scores on the Health Assessment Questionnaire-Disability Index (HAQ-DI) [28], Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [29], and Work Productivity and Activity Impairment (WPAI) scale [30]. Changes from baseline to weeks 12 and 24 in key markers of bone turnover (i.e., CTX, CTX-I, CTX-II, CTX-II CRT, PINP, OPG, sRANKL) were also evaluated as exploratory endpoints. Safety endpoints included AEs, vital signs, and laboratory test results, evaluated by study period and over the entire study.

Statistical Analysis

Screening of 360 subjects and enrollment of 232 were expected. An estimated 45% of enrolled subjects were expected to achieve DAS28-ESR < 3.2 at week 12 and continue on to be randomly assigned in part 2 of the study. On the basis of results from previous studies [31, 32], 80% of the RCI group and 50% of the placebo group were predicted to maintain LDA through week 24 (part 2). A sample size of 52 subjects per treatment group during part 2 was determined to provide 90% power to detect a difference between treatment groups using a two-sided, two-sample comparison of proportions at the significance level of 0.05.

The safety population included all enrolled subjects who received ≥ 1 dose of study drug. All subjects from the safety population who contributed any efficacy data to the study comprised the modified intent-to-treat (mITT) population, which was used for all efficacy analyses. All safety analyses were conducted using the safety population.

Data for all study variables were summarized via descriptive statistics. For the primary endpoint, the proportion of subjects with DAS28-ESR < 3.2 at week 12 (part 1), along with a two-sided 95% confidence interval (CI), was calculated. The study was deemed successful if the lower bound of the 95% CI was ≥ 10%.

The proportions of subjects with LDA defined by CDAI scores ≤ 10 at week 12 and the proportions of subjects who met ACR20, ACR50, or ACR70 criteria at week 12 were analyzed using the same method as the primary endpoint. Changes from baseline to week 12 for the DAS28-ESR, HAQ-DI, FACIT-F, WPAI, tender joint count, swollen joint count, and bone turnover markers were evaluated with one-sample *t* tests.

The proportions of subjects who maintained DAS28-ESR < 3.2 during part 2 (withdrawal phase, weeks 12–24) were compared across treatment groups using a Pearson's Chi-square test, and the proportions of subjects who maintained DAS28-ESR < 2.6 and CDAI scores ≤ 10 and who met ACR20, ACR50, or ACR70 criteria were evaluated similarly. The time to disease activity flare in part 2 was analyzed using a log-rank test. Changes from baseline to week 24 for the DAS28-ESR, HAQ-DI, FACIT-F, WPAI, tender joint count, swollen joint count, and bone turnover markers were assessed via two-sample *t* tests.

RESULTS

Participants

Of 259 enrolled subjects, 235 completed the open-label period and 127 completed the randomized, placebo-controlled, double-blind withdrawal period (Fig. 2). Subject demographics and baseline characteristics are shown in Table 1.

Efficacy: Open-Label Period

At week 12, 163 subjects [62.9% (95% CI 57.3–69.1%)] achieved DAS28-ESR < 3.2, the study's primary endpoint ($p < 0.0001$; Fig. 3a). Figure 3c shows mean DAS28-ESR over time during the open-label period; mean change from baseline to week 12 was − 2.75 [standard deviation (SD), 1.45; $p < 0.001$]. Also at week 12, 169 subjects (65.3%) reached LDA, as defined by a CDAI score ≤ 10 (Fig. 3e), and 83.0% of subjects achieved ACR20, 62.5% achieved ACR50, and 30.1% achieved ACR70 (all $p < 0.0001$; Fig. 3g). Forty-nine subjects (18.9%) achieved DAS28-ESR < 2.6 (i.e., remission) at week 12. Levels of C-reactive protein did not change substantially (Figure S1a in the electronic supplementary material). Significant decreases from baseline in the number of tender and swollen joints were observed (Figure S2a in the electronic supplementary material).

Patient-Reported Outcomes: Open-Label Period

During part 1, open-label RCI therapy led to significant improvements from baseline in HAQ-DI (Figure S3a in the electronic supplementary material) and FACIT-F (Figure S4a in the electronic supplementary material) scores, as well as significant decreases from baseline in

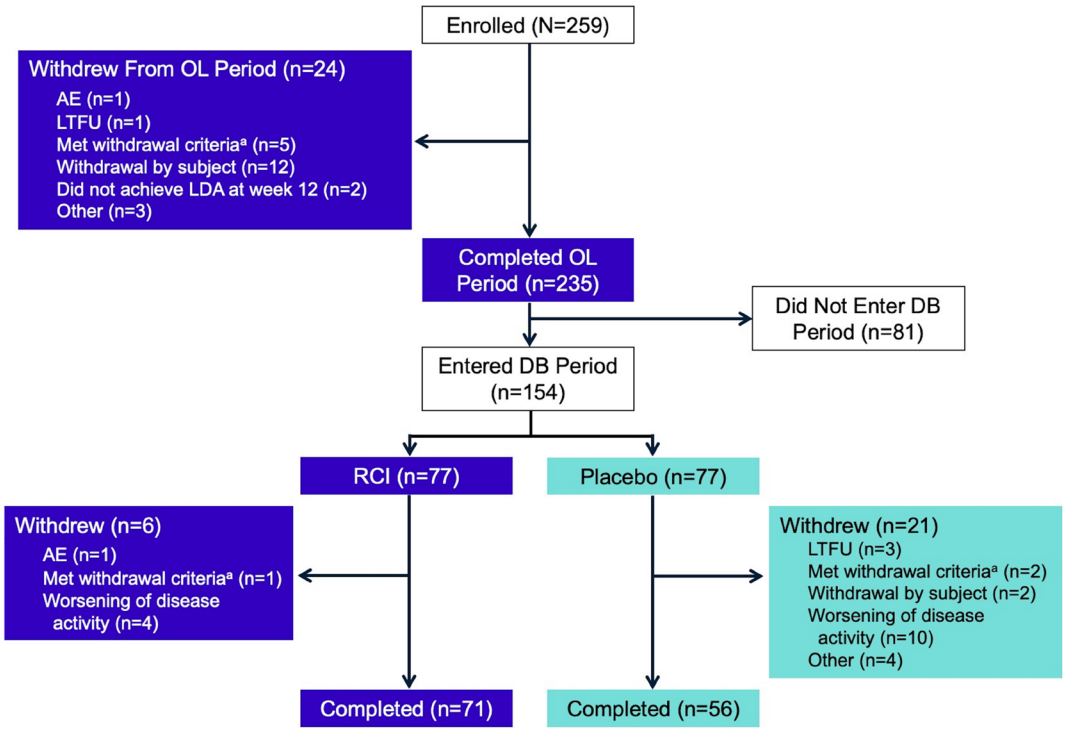

Fig. 2 Subject disposition. [a]Subjects met withdrawal criteria if they developed a condition that met any of the study exclusion criteria or failed to meet any inclusion criteria during the study that was not considered an AE or if they were noncompliant. *AE* adverse event, *DB* double-blind, *LDA* low disease activity, *LTFU* lost to follow-up, *OL* open-label, *RCI* repository corticotropin injection

the percentages of work time missed, impairment while working, overall work impairment, and activity impairment, as assessed via the WPAI (Figure S5a in the electronic supplementary material).

Bone Turnover Markers: Open-Label Period

Most bone turnover markers were stable during the open-label period (Table 2), suggesting a minimal further impact of RCI on bone metabolism in patients already receiving glucocorticoids. At week 12, significant decreases in levels of cartilage degeneration markers CTX-II ($p < 0.01$) and CTX-II CRT ($p < 0.001$) as well as the bone formation marker PINP ($p < 0.01$) were observed, and bone degeneration markers CTX and CTX-I showed no significant changes with RCI treatment in this population.

Efficacy: Double-Blind Withdrawal Period

At week 24, DAS28-ESR LDA was maintained in 47 of 77 (61.0%) RCI-treated subjects and 32 of 76 (42.1%) placebo-treated subjects ($p = 0.019$; Fig. 3b). Mean DAS28-ESR over time during the double-blind period did not differ significantly between treatment groups (Fig. 3d). Mean time to disease activity flare during weeks 12 through 24 was 6.5 weeks (SD, 2.61 weeks) for the placebo group and 8.2 weeks (SD, 2.92 weeks) for the RCI group. At week 24, 66 subjects (85.7%) in the RCI group and 50 (65.8%) in the placebo group maintained LDA, as defined by CDAI scores ≤ 10 ($p = 0.004$; Fig. 3f). A vast majority of subjects achieved ACR20 and ACR50 responses during the open-label period, and these responses were maintained through the double-blind period in both treatment groups; at week 24 of the double-blind period, ACR70 responses were seen in 47% of RCI-treated

Table 1 Subject demographics and baseline characteristics, safety population

Characteristic	Part 1: open-label	Part 2: double-blind	
	RCI (*n* = 259)	Placebo (*n* = 77)	RCI (*n* = 77)
Age, mean (SD), years	51.0 (12.2)	50.9 (11.3)	50.1 (12.2)
Female sex, no. (%)	231 (89.2)	69 (89.6)	67 (87.0)
Race, no. (%)			
White	170 (65.6)	53 (68.8)	53 (68.8)
Black or African American	15 (5.8)	2 (2.6)	1 (1.3)
Asian	3 (1.2)	1 (1.3)	0
American[a] Indian or Alaska native	40 (15.4)	14 (18.2)	12 (15.6)
Native Hawaiian or other Pacific Islander	0	0	0
Other	31 (12.0)	7 (9.1)	11 (14.3)
Ethnicity, no. (%)			
Hispanic or Latino	213 (82.2)	69 (89.6)	73 (94.8)
Country, no. (%)			
United States	88 (34.0)	19 (24.7)	19 (24.7)
Mexico	120 (46.3)	46 (59.7)	41 (53.2)
Argentina	24 (9.3)	7 (9.1)	9 (11.7)
Peru	27 (10.4)	5 (6.5)	8 (10.4)
Weight, mean (SD), kg	72.9 (17.0)	72.4 (14.5)	70.8 (15.7)
BMI, mean (SD), kg/m^2	28.8 (5.7)	29.0 (5.4)	28.2 (5.7)
Disease duration, mean (SD), years	10.3 (8.0)	9.4 (8.8)	10.1 (6.8)
Prednisone (or equivalent) dose, mean (SD), mg/day	6.3 (5.0)	6.9 (8.7)	5.9 (1.7)
Medical history of note, no. (%) [no. ongoing]			
Hypertension	74 (28.6) [73]	20 (26.0) [20]	20 (26.0) [20]
Obesity	6 (2.3) [6]	1 (1.3) [1]	0
Myocardial infarction	2 (0.8) [0]	1 (1.3) [0]	0
Arrhythmia	1 (0.4) [1]	0	0
Cerebrovascular accident	1 (0.4) [0]	0	1 (1.3) [0]
Cerebrovascular disorder	1 (0.4) [0]	1 (1.3) [0]	0
Coronary artery disease	1 (0.4) [1]	0	0
Type 2 diabetes mellitus	1 (0.4) [1]	1 (1.3) [1]	0
Methotrexate use, no. (%)			
Prior	253 (97.7)	77 (100.0)	77 (100.0)
Concomitant	248 (95.8)	77 (100.0)	77 (100.0)

Table 1 continued

Characteristic	Part 1: open-label	Part 2: double-blind	
	RCI (*n* = 259)	Placebo (*n* = 77)	RCI (*n* = 77)
Most common (≥ 3% of subjects) prior DMARDs, no. (%)			
Biologic[b]	60 (23.2)	7 (9.1)	13 (16.9)
Adalimumab	26 (10.0)	3 (3.9)	4 (5.2)
Etanercept	22 (8.5)	1 (1.3)	4 (5.2)
Abatacept	16 (6.2)	1 (1.3)	6 (7.8)
Certolizumab pegol	13 (5.0)	1 (1.3)	2 (2.6)
Tocilizumab	10 (3.9)	0	2 (2.6)
Infliximab	9 (3.5)	1 (1.3)	2 (2.6)
Nonbiologic[c]	232 (89.6)	74 (96.1)	71 (92.2)
Hydroxychloroquine	105 (40.5)	26 (33.8)	39 (50.7)
Sulfasalazine	56 (21.6)	19 (24.7)	10 (13.0)
Leflunomide	53 (20.5)	20 (26.0)	12 (15.6)
Chloroquine	33 (12.7)	13 (16.9)	13 (16.9)
Tofacitinib	8 (3.1)	1 (1.3)	3 (3.9)
Most common (≥ 3% of subjects) concomitant DMARDs, no. (%)			
Biologic[d]	45 (17.4)	9 (11.7)	17 (22.1)
Adalimumab	12 (4.6)	1 (1.3)	1 (1.3)
Certolizumab pegol	9 (3.5)	1 (1.3)	2 (2.6)
Etanercept	9 (3.5)	1 (1.3)	1 (1.3)
Abatacept	8 (3.1)	1 (1.3)	3 (3.9)
Nonbiologic[e]	224 (86.5)	57 (74.0)	59 (76.6)
Hydroxychloroquine	97 (37.5)	25 (32.5)	38 (49.4)
Sulfasalazine	54 (20.9)	19 (24.7)	9 (11.7)
Leflunomide	46 (17.8)	0	0
Chloroquine	33 (12.7)	13 (16.9)	13 (16.9)
DAS28-ESR, mean (SD)	6.3 (1.0)	6.2 (1.0)	6.2 (0.9)
ESR, mean (SD)	43.6 (24.8)	42.0 (22.9)	40.3 (21.5)
DAS28-ESR at week 12, mean (SD)	3.6 (1.4)	2.7 (0.5)	2.8 (0.4)
ESR at week 12, mean (SD)	24.0 (21.5)	15.2 (12.6)	15.8 (12.2)
Tender joint count, mean (SD)[f]	14.7 (7.1)	13.5 (7.2)	13.5 (6.1)
Swollen joint count, mean (SD)[f]	10.9 (5.4)	10.1 (4.9)	9.7 (4.3)

Table 1 continued

Characteristic	Part 1: open-label	Part 2: double-blind	
	RCI (n = 259)	Placebo (n = 77)	RCI (n = 77)
HAQ-DI[f]	1.7 (0.6)	1.7 (0.6)	1.7 (0.5)
FACIT-F[f]	22.8 (8.4)	22.6 (9.0)	22.7 (7.7)

BMI body mass index, *DAS28* Disease Activity Score with 28 joint count, *DMARD* disease-modifying antirheumatic drug, *ESR* erythrocyte sedimentation rate, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *mITT* modified intent-to-treat, *RA* rheumatoid arthritis, *RCI* repository corticotropin injection, *SD* standard deviation

[a] North, Central, or South American Indian

[b] Golimumab, rituximab, clazakizumab, sarilumab, and sirukumab each were taken by < 3% of subjects

[c] Filgotinib was taken by < 3% of subjects

[d] Golimumab, infliximab, and certolizumab each were taken by < 3% of subjects

[e] Tofacitinib was taken by < 3% of subjects

[f] Data are from the mITT population

subjects and 42% of subjects who had discontinued RCI (Fig. 3h). At week 24, 23 subjects (29.9%) in the RCI group and 23 (30.3%) in the placebo group achieved DAS28-ESR remission ($p = 0.828$) in this population with previously highly active RA. Levels of C-reactive protein did not change substantially (Figure S1b in the electronic supplementary material). The mean number of tender and swollen joints remained decreased during the double-blind period, with no significant differences between the RCI and placebo groups noted (Figure S2b-c in the electronic supplementary material).

Patient-Reported Outcomes: Double-Blind Period

Improvements on the HAQ-DI, FACIT-F, and WPAI that were noted during the open-label period were generally maintained in both treatment groups throughout the double-blind period (Figures S3b, S4b, and S5b–e in the electronic supplementary material). There were no significant differences between the RCI and placebo groups on these metrics.

Bone Turnover Markers: Double-Blind Period

Levels of the osteoclast differentiation marker sRANKL significantly increased from baseline to week 12 and week 24 (both $p < 0.05$) in the RCI

Fig. 3 Key efficacy outcomes (mITT population). Proportion of subjects achieving (part 1, open-label period) and maintaining (part 2, double-blind period) key efficacy milestones: LDA (DAS28-ESR < 3.2) (**a**, **b**), CDAI ≤ 10 (**e**, **f**), and ACR criteria (**g**, **h**). Mean DAS28-ESR over time (**c**, **d**). **a** Primary efficacy endpoint. $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$; $^{****}p < 0.0001$ from one-sample binomial test (open-label period) or Pearson's Chi-square test (double-blind period). p values denote differences from baseline for the open-label period and from placebo for the double-blind period. Percentages above bars are rounded to the nearest whole number. *Error bars* are 95% confidence intervals unless otherwise noted. Note: The proportions of subjects meeting ACR50 and ACR70 criteria during part 2 were not prespecified endpoints and were evaluated post hoc. *ACR* American College of Rheumatology, *CDAI* Clinical Disease Activity Index, *DAS28-ESR* Disease Activity Score with 28 joint count erythrocyte sedimentation rate, *LDA* low disease activity, *mITT* modified intent-to-treat, *RCI* repository corticotropin injection, *SD* standard deviation

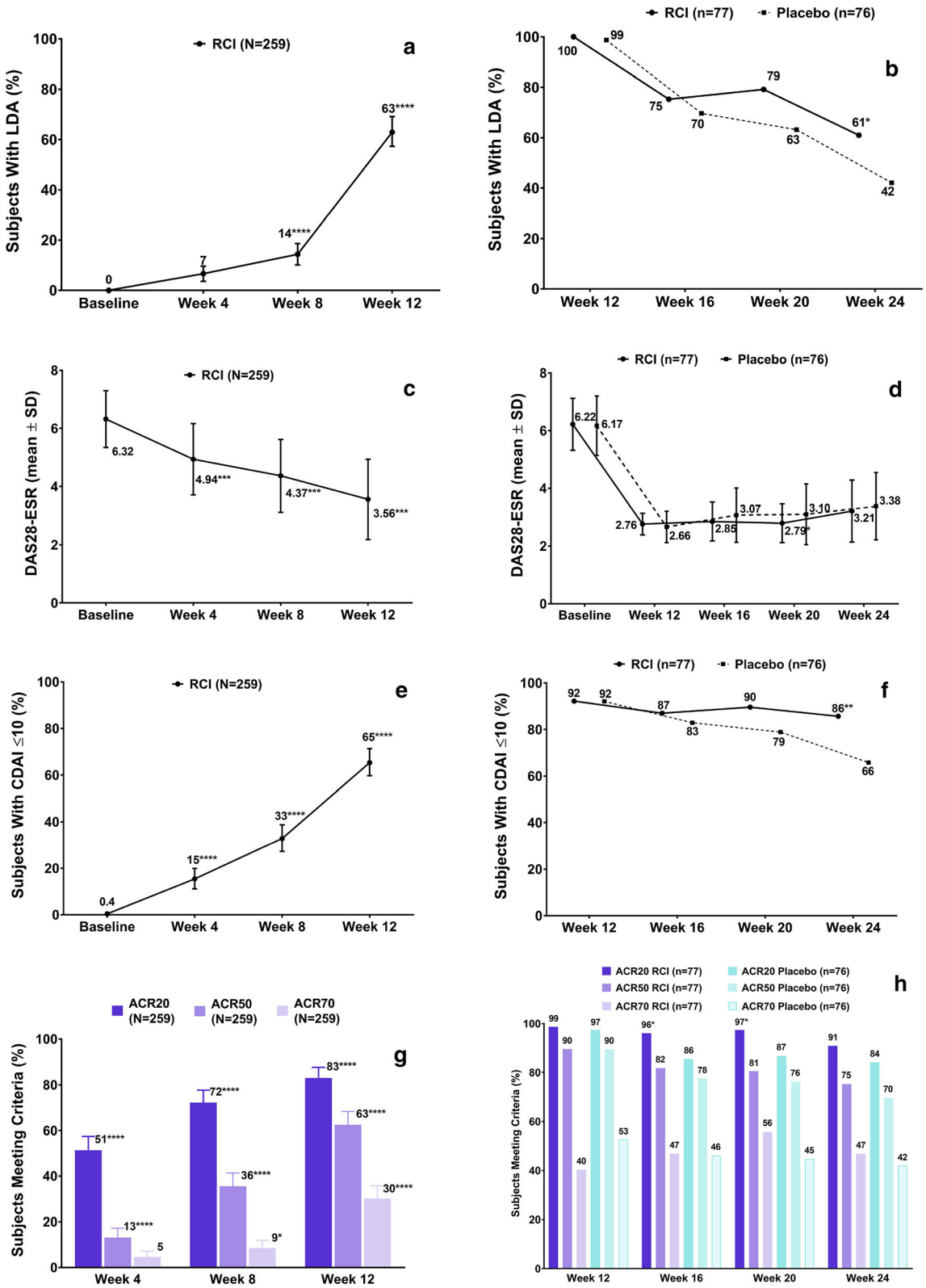
a
RCI (N=259)
Subjects With LDA (%)
0
7
14****
63****
Baseline
Week 4
Week 8
Week 12
b
RCI (n=77)
Placebo (n=76)
Subjects With LDA (%)
100
99
75
70
79
63
61*
42
Week 12
Week 16
Week 20
Week 24
c
RCI (N=259)
DAS28-ESR (mean ± SD)
6.32
4.94***
4.37***
3.56***
Baseline
Week 4
Week 8
Week 12
d
RCI (n=77)
Placebo (n=76)
DAS28-ESR (mean ± SD)
6.22
6.17
2.76
2.66
2.85
3.07
2.79*
3.10
3.21
3.38
Baseline
Week 12
Week 16
Week 20
Week 24
e
RCI (N=259)
Subjects With CDAI ≤10 (%)
0.4
15****
33****
65****
Baseline
Week 4
Week 8
Week 12
f
RCI (n=77)
Placebo (n=76)
Subjects With CDAI ≤10 (%)
92
92
87
83
90
79
86**
66
Week 12
Week 16
Week 20
Week 24
g
ACR20 (N=259)
ACR50 (N=259)
ACR70 (N=259)
Subjects Meeting Criteria (%)
51****
13****
5
72****
36****
9*
83****
63****
30****
Week 4
Week 8
Week 12
h
ACR20 RCI (n=77)
ACR20 Placebo (n=76)
ACR50 RCI (n=77)
ACR50 Placebo (n=76)
ACR70 RCI (n=77)
ACR70 Placebo (n=76)
Subjects Meeting Criteria (%)
99
90
40
97
90
53
96*
82
47
86
78
46
97*
81
56
87
76
45
91
75
47
84
70
42
Week 12
Week 16
Week 20
Week 24

Table 2 Bone turnover markers, mITT population

Time point	Marker, mean (SD)						
	CTX, µg/l	CTX-I, µg/l	CTX-II, µg/l	CTX-II CRT, ng/mmol	OPG, pmol/l	PINP, µg/l	sRANKL, pmol/l
Open-label period							
Baseline[a]	4.79 (2.09)	0.39 (0.21)	3.46 (2.31)	452.4 (325.4)	4.71 (1.80)	52.23 (28.21)	2057.70 (3592.90)
Week 12[b]	4.76 (1.93)	0.39 (0.21)	**2.99[c] (2.17)**	**362.5[d] (273.1)**	4.68 (1.98)	47.37[c] (26.21)	2107.55 (3794.56)
Double-blind period							
Baseline							
RCI[e]	4.77 (1.89)	0.44 (0.22)	3.69 (2.47)	463.7 (316.9)	4.86 (1.83)	54.76 (28.79)	1519.42 (2378.26)
Placebo[f]	4.58 (1.98)	0.38 (0.18)	3.61 (2.42)	460.5 (368.3)	4.65 (1.78)	52.46 (26.38)	2416.34 (3825.88)
Week 12							
RCI[g]	4.58 (1.40)	0.45 (0.23)	2.93 (2.19)	368.0 (228.6)	4.79 (2.23)	51.19 (29.06)	**2451.77[h] (4417.55)**
Placebo[i]	4.61 (1.63)	0.40 (0.21)	3.21 (2.36)	382.5 (257.5)	4.73 (1.89)	48.69 (25.07)	2358.63 (4401.72)
Week 24							
RCI[j]	4.79 (2.76)	0.44 (0.20)	3.13 (1.87)	339.4 (189.7)	4.93 (2.04)	54.34 (40.08)	**2938.96[k] (5006.25)**
Placebo[l]	4.47 (1.68)	0.41 (0.20)	3.27 (2.05)	391.6 (236.0)	5.12 (2.12)	53.10 (26.16)	2105.64 (4116.93)

Bolded values are statistically significant

CTX C-terminal crosslinking telopeptide, *CTX-I* C-terminal crosslinking telopeptide of type I collagen, *CTX-II* C-terminal crosslinking telopeptide of type II collagen, *CTX-II CRT* creatinine-adjusted CTX-II, *mITT* modified intent-to-treat, *OPG* osteoprotegerin, *PINP* N-terminal peptide of type I collagen, *RCI* repository corticotropin injection, *SD* standard deviation, *sRANKL* soluble receptor activator of nuclear kappa B ligand

[a] CTX, $n = 251$; CTX-I and OPG, $n = 254$; CTX-II, $n = 190$; CTX-II CRT, $n = 183$; PINP, $n = 257$; sRANKL, $n = 250$

[b] CTX, $n = 238$; CTX-I, $n = 243$; CTX-II, $n = 159$; CTX-II CRT, $n = 153$; OPG, $n = 239$; PINP, $n = 246$; sRANKL, $n = 231$

[c] $p < 0.01$, one-sample t test for week 12 versus baseline

[d] $p < 0.001$, one-sample t test for week 12 versus baseline

[e] CTX, CTX-I, and PINP, $n = 75$; CTX-II, $n = 59$; CTX-II CRT, $n = 57$; OPG and sRANKL, $n = 73$

[f] CTX, $n = 72$; CTX-I, OPG, and sRANKL, $n = 75$; CTX-II, $n = 59$; CTX-II CRT, $n = 57$; PINP, $n = 76$

[g] CTX, CTX-I, and PINP, $n = 75$; CTX-II, $n = 66$; CTX-II CRT, $n = 64$; OPG, $n = 74$; sRANKL, $n = 72$

[h] $p < 0.05$, two-sample t test for RCI time point versus baseline

[i] CTX, $n = 73$; CTX-I, OPG, and PINP, $n = 74$; CTX-II, $n = 62$; CTX-II CRT, $n = 61$; sRANKL, $n = 71$

[j] CTX, CTX-I, and PINP, $n = 75$; CTX-II and CTX-II CRT, $n = 63$; OPG, $n = 74$; sRANKL, $n = 70$

[k] $p < 0.01$, two-sample t test for RCI time point versus baseline

[l] CTX, CTX-I, OPG, and PINP, $n = 65$; CTX-II, $n = 46$; CTX-II CRT, $n = 45$; sRANKL, $n = 61$

group, but not in the placebo group (Table 2). All other bone turnover markers remained stable.

Safety

During the open-label period, 43 subjects (16.6%) reported treatment-related AEs; nine subjects (11.7%) in the RCI group and ten (13.0%) in the placebo group reported treatment-related AEs during the double-blind period (Table 3). Adverse events that are typically associated with corticosteroid use (e.g., hypertension, hyperglycemia, headache, weight gain, edema) were low in incidence or not reported at all. Three subjects (1.2%) reported serious AEs, all during the open-label period. One case each of chest pain and craniocerebral injury were considered unrelated to treatment. One case of pneumonia was considered possibly related to treatment; RCI therapy was discontinued, and the patient recovered. No subjects died during the study.

Table 3 Summary of AEs, safety population

Part 1 (open-label period)	
AE	**No. (%) of patients RCI (*n* = 259)**
Any AE[a]	98 (37.8)
Anemia	5 (1.9)
Glycosylated hemoglobin increased	4 (1.5)
Headache	9 (3.5)
Hypertension	4 (1.5)
Nasopharyngitis	4 (1.5)
Nausea	5 (1.9)
Pharyngitis	7 (2.7)
Upper respiratory tract infection	4 (1.5)
Urinary tract infection	10 (3.9)
AE resulting in study drug withdrawal	3 (1.2)
Serious AE	3 (1.2)
Serious infectious event	1 (0.4)
Opportunistic infections	
Herpes zoster	1 (0.4)
Tuberculosis	0
Death	0

Part 2 (double-blind period)		
AE	**No. (%) of patients**	
	Placebo (*n* = 77)	**RCI (*n* = 77)**
Any AE[a]	31 (40.3)	25 (32.5)
Anemia	2 (2.6)	2 (2.6)
Back pain	0	2 (2.6)
Diarrhea	3 (3.9)	1 (1.3)
Dizziness	1 (1.3)	1 (1.3)
Gastritis	2 (2.6)	1 (1.3)
Glycosylated hemoglobin increased[b]	2 (2.6)	1 (1.3)

Table 3 continued

Part 2 (double-blind period)		
AE	**No. (%) of patients**	
	Placebo (*n* = 77)	**RCI (*n* = 77)**
Headache	5 (6.5)	5 (6.5)
Hyperglycemia	2 (2.6)	3 (3.9)
Hypertension	0	3 (3.9)
Influenza	1 (1.3)	1 (1.3)
Nasopharyngitis	2 (2.6)	2 (2.6)
Rhinitis	2 (2.6)	0
Upper respiratory tract infection	3 (3.9)	0
Urinary tract infection	3 (3.9)	2 (2.6)
AE resulting in study drug withdrawal	1 (1.3)	0
Serious AE	0	0
Serious infectious event	0	0
Opportunistic infections		
Herpes zoster	0	0
Tuberculosis	0	0
Death	0	0

AE adverse event, *RCI* repository corticotropin injection
[a] AEs reported in ≥ 1.5% of subjects in part 1 or in either group in part 2 are listed below
[b] Refers to glycosylated hemoglobin values > 6.5%

DISCUSSION

These results support the efficacy of RCI in patients with continued highly active RA despite treatment with prednisone and one or two DMARDs, which could include a bDMARD. Despite a mean baseline DAS28-ESR of 6.3, 63% of patients achieved DAS28-ESR < 3.2 by week 12, with a statistically significant percentage achieving LDA by week 8. Thus, the study's primary endpoint was met (Fig. 3a). These results were confirmed by the proportions of subjects who achieved CDAI ≤ 10 (Fig. 3e) and

ACR20, ACR50, and ACR70 responses (Fig. 3g) during the open-label period.

During the double-blind period, DAS28-ESR LDA was maintained in almost two-thirds of subjects who continued RCI. Of importance, > 40% of patients who withdrew from RCI to placebo maintained LDA for an additional 12 weeks (Fig. 3b). These results suggest that patients with high disease activity despite treatment with glucocorticoids and a csDMARD (with or without a bDMARD) or a bDMARD as monotherapy may have a clinically meaningful decrease in disease activity with RCI treatment for a period of 3 months, which may be maintained even after RCI treatment withdrawal. Interestingly, when LDA was assessed by CDAI ≤ 10 (Fig. 3d), 86% of subjects who continued on RCI maintained LDA, and almost two-thirds of subjects who withdrew RCI maintained LDA. Disparity in the durability of response as assessed by DAS28-ESR versus by CDAI is most likely explained by differences in the contribution of various elements to these metrics. Although both the DAS28 and the CDAI assess tender and swollen joints, these factors are given equal weight in calculation of CDAI scores, whereas tender joint counts are given twice the weight of swollen joints in calculation of the DAS28-ESR [25, 33]. Importantly, the CDAI does not assess ESR, an acute phase reactant, whereas the DAS28-ESR does.

Achievement and maintenance of remission, or at least LDA, should be the primary approach for RA, but assessment of physical functioning, disability, and other health outcomes also provides important information for the overall evaluation of a drug's benefit. During the open-label period, improvements were seen in several patient-reported outcomes assessing disability (HAQ-DI), fatigue (FACIT-F), and work/activity (WPAI). These improvements were generally maintained during the double-blind withdrawal period in both treatment groups, which further supports the suggestion that the benefits of RCI may be maintained for some time after treatment is discontinued.

No unexpected safety signals were observed during the study. The three serious AEs reported in patients receiving RCI were consistent with those previously reported with RCI therapy. The incidences of AEs commonly associated with corticosteroids were low and typically similar in the RCI and placebo groups, which suggests the possibility of minimal additional steroidal effects of RCI in patients already on glucocorticoids. One might expect a greater incidence of common corticosteroid-associated AEs if RCI therapy were continued indefinitely, but extension studies and/or registries would be needed to evaluate the safety of long-term RCI therapy. Markers of bone turnover were mostly stable during both study periods, indicating no pronounced additional effect of RCI on bone metabolism in patients who had been receiving 5 to 10 mg/day of prednisone (or equivalent) for ≥ 4 weeks. In the open-label period, cartilage degeneration markers showed a significant decrease from baseline at week 12; although the bone formation marker PINP significantly decreased, this may not be indicative of bone loss, especially because bone degeneration markers remained stable. During the double-blind period, levels of osteoclast marker sRANKL significantly increased from baseline to weeks 12 and 24 in the RCI group but not the placebo group. However, this may not suggest evidence of bone damage, as bone degeneration marker levels remained stable. The role of RCI and bone turnover in a population already receiving glucocorticoids over a prolonged period still needs to be evaluated.

Results from this study suggest a role for RCI in treating patients who have active RA with at least moderate disease activity despite maximal treatment with DMARDs, whether csDMARDs or bDMARDs, and who are also being treated with glucocorticoids. In previous studies, including the COBRA study [34] and other similar trials, high- or moderate-dose glucocorticoids were used in the initiation of therapy (with subsequent tapering) to quickly obtain disease control. In contrast, RCI was used not as initial therapy but rather as rescue therapy in the current study while low/moderate-dose glucocorticoids were maintained. Assuming the patient has been maximally treated with DMARDs, a potential treatment scenario might involve 3 months of RCI therapy with the aim of achieving remission or LDA. Results from this study suggest that such patients with

recalcitrant disease may respond well to RCI therapy and that some patients will maintain LDA after discontinuation of RCI therapy. Thus, it is at the discretion of the physician whether to discontinue RCI therapy at 3 months, with subsequent monitoring to assess whether response is maintained. For patients who develop a flare after RCI discontinuation, the consideration of additional RCI therapy for flares when they occur may be reasonable if long-term safety findings support such an approach. The effects of long-term RCI therapy on bone health and other aspects of safety are unclear and require further study, but the results from this study suggest that RCI could be used in an intermittent manner for many patients without significant concerns about general safety or bone loss. For patients who have flares shortly after discontinuation of RCI therapy, the risk–benefit for prolonged use of RCI still needs to be defined.

This study has some notable limitations. Although we used a study design that has previously been employed successfully [35], the primary endpoint was measured in the open-label period, during which all subjects knew that they were being treated with RCI. The response observed for this endpoint in this population with recalcitrant disease was higher than expected, which could, in part, be a result of the study design (i.e., a placebo effect). However, it would be unusual for a placebo effect to manifest after 8 weeks, as it was in this study (Fig. 3a, e). In addition, the vast majority (> 80%) of study participants were of Hispanic or Latino ethnicity, which may limit extrapolation of the results to the general population. It is also worth noting that patients with other rheumatic autoimmune diseases, clinically significant infections, or malignancies were excluded from the study. Caution should be observed in extrapolating the study's safety results to such populations. Also, bone density testing was not performed in this study but would be reasonable to evaluate in future studies, considering the association between glucocorticoid therapy and the development of osteoporosis. Finally, participants in the current study had highly active RA despite treatment with DMARDs and glucocorticoids, and changes in these baseline therapies were not allowed during the study in order to properly assess the rescue effects of RCI. Current guidelines from EULAR [36] and ACR [4] recommend that glucocorticoids be used at the lowest possible dose and tapered as soon as feasible. Future studies with additional treatment arms wherein tapering of glucocorticoids and/or DMARD adjustments are allowed may be warranted.

Despite these limitations, the randomized, double-blind, placebo-controlled withdrawal period of this study provided a more rigorous assessment of the efficacy and safety of RCI.

CONCLUSIONS

The results of this study of patients who had active RA despite corticosteroid/DMARD therapy show that patients can achieve LDA as early as week 8. By week 12, more than half of the subjects achieved LDA, which was maintained with an additional 12 weeks of treatment. Importantly, many subjects who achieved LDA with RCI therapy and then discontinued RCI use during the withdrawal period were able to maintain LDA for the subsequent 3 months, which may suggest sustained durability of RCI therapy. No new unexpected safety signals were noted, and markers of bone turnover were mostly stable, suggesting that RCI does not cause further bone loss in patients with active RA previously treated with glucocorticoids.

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Compliance with Ethics Guidelines. The study was conducted at 60 centers in four countries (see electronic supplementary material for details on study centers) from November 7, 2016, to February 13, 2019, in accordance with the principles and requirements of the Declaration of Helsinki, Good Clinical Practices, and clinical trial registration (clinicaltrials.gov identifier NCT02919761). All investigators obtained institutional review board/independent ethics committee approval. All subjects provided informed consent (including consent for publication) before any study procedures were performed.

Data Availability. The discussion of statistical endpoints and analysis is included in this manuscript. Summary aggregate results, including AE information and the study protocol, will be available by December 2019 on ClinicalTrials.gov (NCT02919761). Individual patient data will not be disclosed unless requested, allowed per informed consent, and appropriately anonymized. Requests for additional information should be directed to Mallinckrodt Pharmaceuticals' Department for Clinical Trial Disclosure and Transparency at clinicaltrials@mnk.com.

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