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ORIGINAL RESEARCH

Results From a Phase 4, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Repository Corticotropin Injection for the Treatment of Pulmonary Sarcoidosis

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ABSTRACT

Introduction: Long-term treatment of pulmonary sarcoidosis with glucocorticoids has been associated with toxicity and other adverse events, highlighting the need for alternative therapies. The goal of this study was to evaluate the efficacy and safety of repository corticotropin injection (RCI, Acthar® Gel) in patients with pulmonary sarcoidosis and to validate endpoints for use in future clinical trials.

Methods: In this multicenter, randomized, placebo-controlled trial, subjects received subcutaneous RCI (80 U) twice weekly or matching placebo through 24 weeks in a double-blind treatment phase, followed by an optional 24-week open-label extension. Efficacy was measured by glucocorticoid tapering, pulmonary function tests, chest imaging, patient-reported outcomes, and a novel sarcoidosis treatment score (STS). Safety was assessed by adverse events, physical examinations, vital signs, clinical laboratory abnormalities, and imaging. The study was terminated early due to low enrollment caused by the COVID-19 pandemic, thereby precluding statistical analysis.

Results: Fifty-five subjects were randomized to receive either RCI ($n = 27$) or placebo ($n = 28$). Mean STS at week 24 showed greater improvement with RCI (1.4) compared with placebo (0.7). At week 48, those who remained on RCI had an STS of 1.8 compared with 0.9 in those who switched from placebo to RCI. More subjects in the RCI group discontinued glucocorticoids at week 24 compared to the placebo group. Glucocorticoid discontinuation was comparable at week 48 for those who switched from placebo to RCI and those who continued RCI. Similar trends in favor of RCI over placebo were observed with the other efficacy endpoints. No new or unexpected safety signals were identified.

Conclusions: RCI was safe and well tolerated, with trends in efficacy data suggesting greater improvement with RCI compared to placebo in patients receiving standard-of-care therapy for pulmonary sarcoidosis. The study also provided validation of efficacy endpoints that may be used in larger trials for pulmonary sarcoidosis.

Trial registration: ClinicalTrials.gov identifier: NCT03320070.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41030-023-00222-2.

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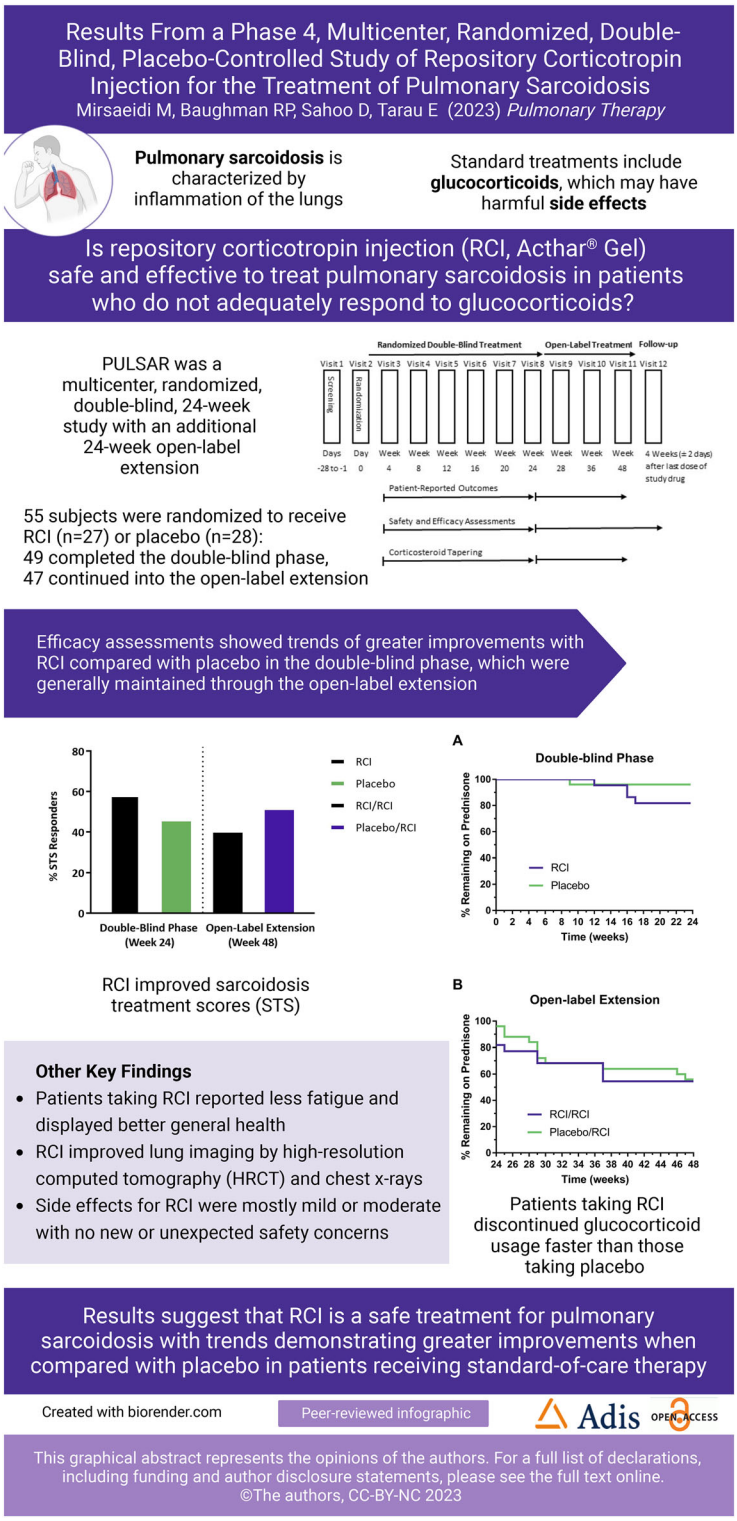
Graphical Abstract:



PLAIN LANGUAGE SUMMARY

Pulmonary sarcoidosis is a disease characterized by inflammation of the lungs. Standard treatments include glucocorticoids, which may have harmful side effects. This clinical trial investigated whether repository corticotropin injection (RCI, Acthar® Gel) was safe and effective in patients who were already taking glucocorticoids to treat pulmonary sarcoidosis. Patients were randomly assigned to be in one of two treatment groups: RCI or placebo. In the first 24 weeks of the study, 27 patients were injected with RCI twice weekly, while 28 patients were injected with an inactive substance (placebo). Forty-seven patients continued into an optional phase of the study for an additional 24 weeks in which all patients received RCI twice weekly. A sarcoidosis treatment score and assessments of lung health, general health, and fatigue were used to determine whether RCI was effective. These assessments showed greater improvements with RCI compared to placebo. Patients who switched from placebo to RCI showed similar improvements to those who remained on RCI throughout the entire study. Patients receiving RCI were able to discontinue their use of glucocorticoids more quickly than those taking placebo, thus helping them to avoid the harmful side effects of the glucocorticoids. Side effects for RCI were mostly mild or moderate, and no new or unexpected safety concerns for RCI were seen throughout the study.

Keywords: Acthar Gel; Clinical trial; Pulmonary sarcoidosis; RCI; Repository corticotropin injection

Key Summary Points

This study sought to evaluate the safety and efficacy of repository corticotropin injection (RCI, Acthar® Gel) in patients receiving standard-of-care therapies for pulmonary sarcoidosis and to validate several endpoints for use in future trials, including a novel composite sarcoidosis treatment score, pulmonary function tests, chest imaging, patient-reported outcomes, and changes in glucocorticoid dosing regimen.

RCI was well tolerated, and efficacy assessments showed trends of greater improvement with RCI compared with placebo in the double-blind phase of the study, which were generally maintained through the open-label extension, and patients who switched from placebo to RCI in the open-label phase showed improvements in most efficacy endpoints; more rapid discontinuation of glucocorticoids was observed with RCI treatment compared with placebo, demonstrating a glucocorticoid-sparing effect for RCI.

These results suggest that RCI may be safe and effective for the treatment of pulmonary sarcoidosis in patients receiving standard-of-care therapy.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/https://figshare.com/s/17a433ea2a6f5a8c4518.

INTRODUCTION

Sarcoidosis is a chronic, noncaseating, granulomatous condition of unclear etiology that may involve multiple organs and affects the lungs in 80–90% of cases [1–7]. The prevalence

of sarcoidosis in the US is estimated to be 60 per 100,000 adults, which varies by geographic region, ethnicity, age, and sex [3, 8]. A third to half of patients with non-progressive, asymptomatic pulmonary sarcoidosis may not require systemic therapy and may show spontaneous remission [9]. However, many patients with the lung disease may experience progression, and pharmacologic treatment is utilized [1].

Therapeutic goals for severe pulmonary sarcoidosis include reduction of granulomatous inflammation and prevention of irreversible organ damage while averting toxicity from medications [1]. Severe disease may also require addition of immunomodulators or biologics. Oral glucocorticoids are approved by the US Food and Drug Administration (FDA) for treatment of symptomatic pulmonary sarcoidosis and remain the standard-of-care first-line treatment to disrupt granuloma formation and protect organ function [1, 10, 11]. However, long-term high-dose glucocorticoid use is associated with toxicity and adverse events (AEs), highlighting the need for alternative therapies [12].

Repository corticotropin injection (RCI, Acthar® Gel) is the only other medication approved by the FDA for the treatment of symptomatic pulmonary sarcoidosis and should be considered on a case-by-case basis [1, 10]. RCI is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogs and other pituitary peptides [13]. ACTH and other melanocortin receptor (MCR) agonists are known to have anti-inflammatory effects [14–16]. The mechanism of action of RCI is thought to be via activation of MCRs 1 through 5, which are expressed in a variety of cell types including immune cells found in granulomas [17]. The anti-inflammatory effect of RCI may be partly mediated through stimulation of cortisol production from the adrenal cortex via MC2R but also through activation of MC1R, MC3R, and MC5R on immune cells [15, 18]. RCI has its weakest full agonistic activity at MC2R and stimulates cortisol induction only slightly above normal endogenous levels [19]; notably, the effects of RCI were not mimicked by synthetic $ACTH_{1\text{-}24}$ depot, which showed its highest agonistic activity at MC2R and much higher cortisol induction [19]. RCI has been shown to reduce proliferation of B cells and antibody production [20] and to decrease inflammatory cytokine production from macrophages and T cells [21, 22]. A recent study demonstrated anti-inflammatory activity of an MCR agonist (α-melanocyte stimulating hormone) using in vitro and in vivo sarcoid-like granuloma models [14].

Clinical studies have demonstrated the effectiveness of RCI for the treatment of pulmonary sarcoidosis. In a retrospective chart review, RCI treatment for at least 3 months' duration was associated with clinical improvement in 11 of 29 (38%) patients [7]. A small prospective study assessing RCI for chronic pulmonary sarcoidosis noted improvements in disease assessments and a significant reduction of prednisone dose in 16 patients who completed 24 weeks of RCI therapy [23]. A large analysis of medical records for patients with advanced sarcoidosis ($n = 302$) found overall status improvement in 95% of patients and reduction of glucocorticoid use from 61.3% at the initiation of treatment to 12.9% after 3 months of RCI therapy [24].

A major challenge in clinical trials for pulmonary sarcoidosis is the current lack of well-characterized, standardized endpoints for assessing efficacy. The objective of this clinical trial was to evaluate the efficacy and safety of RCI in the treatment of pulmonary sarcoidosis and to validate various endpoints for use in future trials including glucocorticoid tapering, pulmonary function tests, lung imaging, patient-reported outcomes, and a novel sarcoidosis treatment score (STS) based on a composite of endpoint components in pulmonary sarcoidosis patients treated with RCI for 24–48 weeks.

METHODS

Study Design

PULSAR was a phase 4, multicenter, randomized, double-blind (DB), placebo-controlled study with subjects assigned in a 1:1 ratio using a computer-generated, block-randomized allocation scheme to receive 80 U subcutaneous

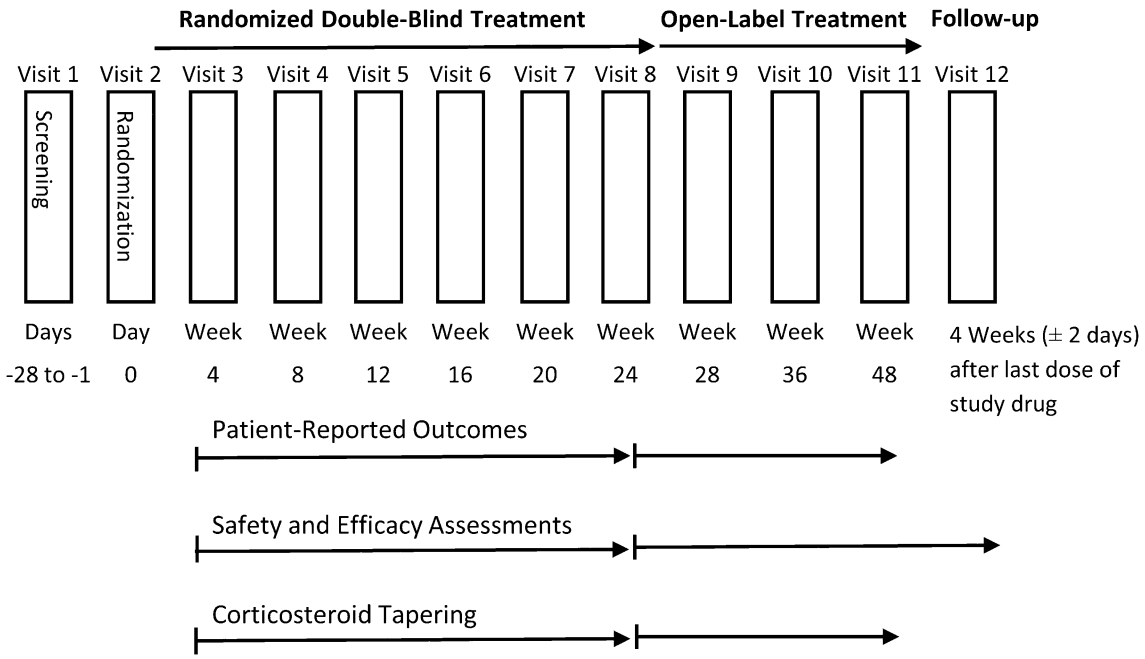


Fig. 1 PULSAR study design overview

(SC) RCI twice weekly or matching placebo in addition to standard-of-care medications including but not limited to glucocorticoids, methotrexate, and azathioprine. The biostatistician implemented the randomization scheme; investigators, radiologists, and subjects were unaware of the treatment assignment. The study consisted of screening up to 28 days, DB treatment for 24 weeks, and an optional 24-week open-label extension (OLE) during which all participating subjects received 80 U SC RCI twice weekly, regardless of whether they received RCI or placebo in the DB phase (Fig. 1). A follow-up visit was conducted 4 weeks after the final dose of RCI was administered. During each visit following randomization, glucocorticoid tapering was evaluated and implemented based on a protocol-specified algorithm through week 48. The study began randomization in February 2018 and was completed by June 2020.

Ethics

This study was performed in accordance with the ethical principles originating from the Declaration of Helsinki and in full compliance with applicable international, national, and local regulatory requirements. The protocol was approved by each research facility's Institutional Review Board/Independent Ethics Committee, and all subjects provided informed consent prior to performance of any study-related procedures. The study is registered on ClinicalTrials.gov (NCT03320070).

Subject Selection

Patients diagnosed with pulmonary sarcoidosis were screened for enrollment with the following key inclusion criteria: male or female adults $\geq$ 18 and $\leq$ 90 years of age at screening; female subjects without childbearing potential, who were postmenopausal, or who agreed to use effective contraception throughout the study; subjects willing to follow all protocol requirements and self-inject SC RCI or have a caregiver do so; those who were willing and able to return for all study visits; those diagnosed with biopsy-confirmed sarcoidosis meeting American Thoracic Society criteria with onset $\geq$ 1 year prior to screening [25]; those

with symptomatic pulmonary disease; those on a stable prednisone dose ≥ 4 weeks prior to screening, with dosages 5–40 mg/d; and those who, if treated with any disease-modifying anti-sarcoidosis drugs, were on a stable dose for ≥ 3 months prior to screening.

Patients were excluded from enrollment for any of the following reasons: history of sensitivity to ACTH preparations or sensitivity to porcine protein products; pulmonary arterial hypertension requiring or receiving treatment; extrapulmonary involvement that would impede glucocorticoid tapering; treatment with anti–tumor necrosis factor-α antibody in the prior 3 months; known contraindication(s) to RCI; clinically significant infection requiring intravenous antibiotics or hospitalization in the 4 weeks prior to screening or between screening and first dose of the test drug; known immune-compromised status not related to the disease/condition under study; solid tumor malignancy or hematologic malignancy currently diagnosed or undergoing therapy or having received therapy in the previous 5 years; and history of use of ACTH preparations for treatment of sarcoidosis. The planned sample size was 100 subjects who would be randomly assigned receive either RCI or placebo (1:1 ratio). No formal sample size calculations were performed; instead, the sample size was based on recent literature of comparative studies in sarcoidosis [26–28].

Treatment Regimens

For the DB phase, subjects were administered 80 U (1 ml) RCI or placebo (1 ml) SC twice weekly for 24 weeks. Placebo was identical to RCI (including 16% gelatin and 0.5% phenol) without the active medication. Patients who received either RCI or placebo were given the option to enter the OLE, in which all subjects received 80 U RCI SC twice weekly for 24 additional weeks. The RCI dosing regimen was determined by patterns of clinical use in the treatment of sarcoidosis and the package insert [7, 13, 23].

Efficacy and Safety Assessments

The modified intent-to-treat population included all subjects who received at least 1 dose of RCI and contributed any efficacy data to the study. Efficacy assessments included extent of glucocorticoid tapering, pulmonary function tests [percentage predicted forced vital capacity (FVC) and percentage predicted diffusing capacity of the lungs for carbon monoxide (DLCO)], high-resolution computed tomography (HRCT) and chest X-rays, patient-reported quality-of-life outcomes (King's Sarcoidosis Questionnaire and Fatigue Assessment Scale), and a newly developed composite STS. The STS could range from − 6 to + 6, with higher scores indicating greater improvement (Supplemental Table S1). STS for each subject was determined after completion of the DB phase (week 24) and at the end of the OLE (week 48). A response was defined as an STS score of ≥ + 3 points, while a partial response was + 2 points or stable disease with glucocorticoid reduction (i.e., a total STS score of + 1 due to ≥ 50% reduction in glucocorticoid dosage). Non-response was defined as an STS score of ≤ + 1 points with no glucocorticoid taper. Subjects were categorized as STS responders if they exhibited a response or partial response to treatment. Safety was assessed by the incidence, severity, and relationship of AEs, physical examinations, vital signs, clinical laboratory abnormalities, and imaging. HRCT and chest X-ray imaging results were evaluated by the board-certified investigator/radiologist and the central reader using side-by-side comparisons to determine whether the patient's condition had improved, stabilized, or deteriorated based on a 5-point Likert scale ranging from much worse to worse, unchanged, better, or much better, which has been previously used in other studies [29, 30]. The safety population included all subjects who received at least 1 dose of RCI.

Statistical Analysis

Summary descriptive statistics were determined for all numerical (or continuous) variables. Frequencies and percentages were calculated for

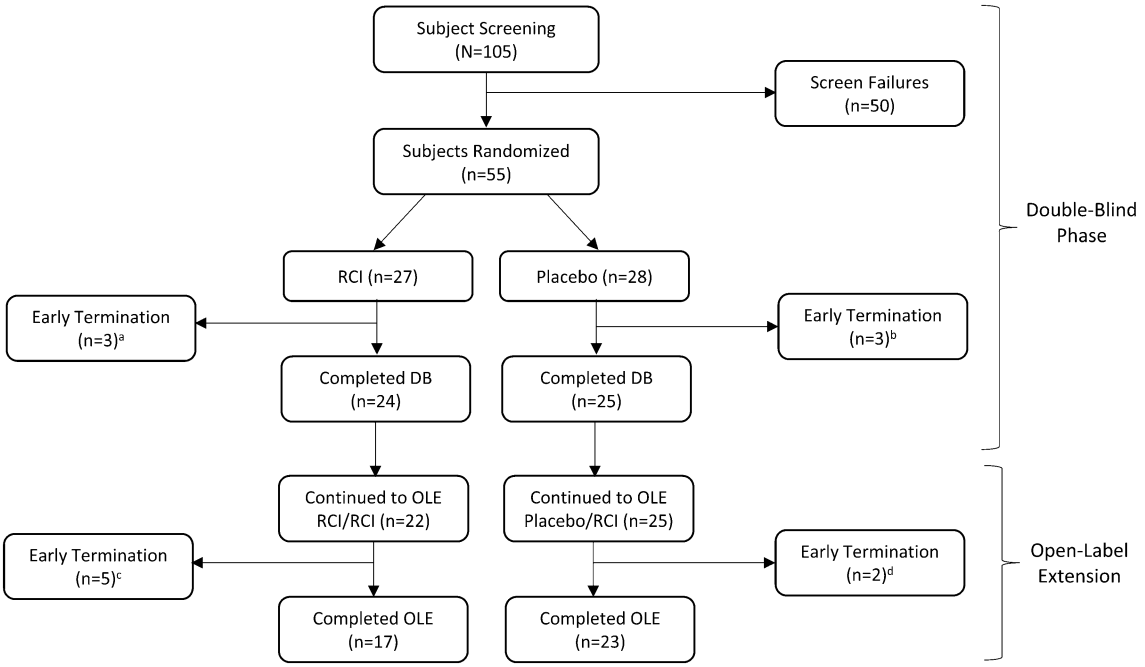


Fig. 2 Subject flow (CONSORT) diagram. *DB* indicates double-blind phase, *OLE* open-label extension, *RCI* repository corticotropin injection.[a]Withdrawal by subject (n = 2) and an adverse event of worsening diabetes (n = 1).[b]Withdrawal by subject (n = 2) and an adverse event of allergic reaction at injection site (n = 1).[c]Withdrawal by subject (n = 1), non-compliance (n = 1), and adverse events (n = 3).[d]Withdrawal by subject (n = 1) and loss to follow-up (n = 1)

categorical variables. Time-to-event endpoints were assessed with log-rank tests and generation of Kaplan–Meier curves. SAS® version 9.4 (SAS Institute, Inc.) was used for all analyses. This study was not sufficiently powered to determine statistical significance between treatment groups due to the reduced sample size from low enrollment caused primarily by the COVID-19 pandemic.

Post Hoc Subgroup Analysis

Post hoc subgroup analysis was performed to investigate STS response in subjects based on the individual parameters composing the STS including time since diagnosis; baseline prednisone dose; FVC, DLCO, and King's Sarcoidosis General Health scores; and lung-only vs. multi-organ involvement. The Extrapulmonary Physician Organ Severity Tool (ePOST), which evaluates 17 extrapulmonary organs, was used during the study to determine the absence or presence and severity of multi-organ pathology [31]. The proportions of STS responders were determined for subgroups of RCI and placebo cohorts at week 24, along with odds ratios and corresponding 95% confidence intervals (CIs) calculated with an asymptotic model.

RESULTS

Subject Disposition

A total of 55 subjects were randomized to receive RCI (n = 27) or placebo (n = 28), with 49 completing the DB phase and 47 continuing into the OLE (Fig. 2). Early termination from the DB phase included four withdrawals and two discontinuations due to AEs (worsening diabetes and injection site reaction). Forty subjects completed the OLE phase, including those who received RCI in both phases [RCI/RCI (n = 17)] and subjects who had placebo in the

Table 1 Baseline demographics and clinical characteristics

Parameter	RCI (n = 27)	Placebo (n = 28)	Total (N = 55)
Age (years), mean (SD)	53.6 (9.1)	54.8 (11.3)	54.2 (10.2)
Sex, n (%)			
Male	16 (59.3)	13 (46.4)	29 (52.7)
Female	11 (40.7)	15 (53.6)	26 (47.3)
Race, n (%)			
White	21 (77.8)	15 (53.6)	36 (65.5)
Black/African American	6 (22.2)	13 (46.4)	19 (34.5)
Ethnicity, n (%)			
Hispanic or Latino	4 (14.8)	4 (14.3)	8 (14.5)
Non-Hispanic or Latino	23 (85.2)	24 (85.7)	47 (85.5)
Body mass index (kg/m^2), mean (SD)	34.4 (7.3)	33.1 (7.4)	33.7 (7.3)
Time since sarcoidosis diagnosis (months), mean (SD)	109.4 (96.6)	112.3 (97.1)	110.8 (96.0)

RCI repository corticotropin injection, *SD* standard deviation

DB phase and then switched to RCI in the OLE [placebo/RCI n = 23)]. Eight patients discontinued the study drug during the OLE due to AEs (n = 4) including diabetes mellitus, pulmonary fibrosis, pulmonary embolism, and respiratory failure; subject withdrawal (n = 2); loss to follow-up (n = 1); or non-compliance with the study drug (n = 1).

Baseline Demographics and Clinical Characteristics

Demographics and characteristics were similar for the RCI and placebo groups (Table 1). Subjects were predominantly White (65.5%) and non-Hispanic/Latino (85.5%). Mean age was 54.2 years, and approximately half of the subjects were male (52.7%). Mean time of disease duration between diagnosis of sarcoidosis and screening for the safety population was 110.84 months. Lung manifestations were present in 100% of subjects. The most frequently involved extrapulmonary organs (> 15%) included bone/joint (23.6%), skin (25.5%), eyes (18.2%), and liver (18.2%). Prior and concomitant systemic glucocorticoids were used in 100% of subjects.

Glucocorticoid Tapering

The mean overall percentage change from baseline of weekly average prednisone or equivalent daily dose was similar between treatment groups at weeks 24 and 48 (Table 2). However, the time at which subjects' glucocorticoid dose was discontinued with no relapse was substantially different at week 24, as a larger proportion of subjects in the RCI cohort had their glucocorticoids discontinued relative to the placebo cohort. After all subjects began receiving RCI during the OLE, those who had been on placebo in the DB phase showed similar results at week 48 compared to those who received RCI in both phases (Fig. 3).

STS Evaluation

The mean STS at week 24 was two-fold higher in the RCI group (1.4) compared to the placebo group (0.7), suggesting greater improvement when patients were given RCI. Similar results

Table 2 Efficacy results for STS, pulmonary function tests, and patient-reported outcomes

Parameter	Double-blind phase (week 24)		Open-label extension (week 48)	
	RCI	Placebo	RCI/RCI	Placebo/RCI
Prednisone taper, % change from baseline[a] (95% CI)	− 57.3 (− 71.2 to − 43.4); *n* = 25	− 58.6 (− 70.5 to − 46.7); *n* = 25	− 75.7 (− 90.5 to − 60.95); *n* = 18	− 70.1 (− 86.6 to − 53.6); *n* = 23
Baseline mean prednisone dose, mg (95% CI)	14.5 (11.5 to 17.5); *n* = 27	11.6 (8.8 to 14.5); *n* = 28	15.7 (12.2 to 19.2); *n* = 22	11.8 (8.6 to 15.0); *n* = 25
Final mean prednisone dose, mg (95% CI)	7.3 (3.5 to 11.1); *n* = 25	4.9 (3.1 to 6.7); *n* = 25	5.3 (1.1 to 9.4); *n* = 18	3.4 (1.6 to 5.2); *n* = 23
STS, mean (SD) [95% CI]	1.4 (2.2) [0.5 to 2.3]; *n* = 25	0.7 (2.3) [− 0.2 to 1.6]; *n* = 23	1.8 (2.0) [0.8 to 2.8]; *n* = 15	0.9 (2.2) [− 0.1 to 1.9]; *n* = 20
Lung FVC				
Mean (SD) [95% CI] change from baseline	2.74 (5.2) [0.6 to 4.9]; *n* = 23	2.41 (7.6) [− 0.8 to 5.6]; *n* = 22	1.14 (4.7) [− 1.2 to 3.4]; *n* = 16	3.30 (8.9) [− 0.6 to 7.2]; *n* = 20
Improvement ≥ 5%, *n* (%)	10 (37.0); *n* = 27	7 (25.0); *n* = 28	2 (12.5); *n* = 16	6 (30.0); *n* = 20
Lung DLCO				
Mean (SD) [95% CI] change from baseline	− 1.42 (15.5) [− 7.8 to 4.9]; *n* = 23	− 2.40 (11.6) [− 7.3 to 2.5]; *n* = 22	3.71 (12.0) [− 2.2 to 9.6]; *n* = 16	− 2.40 (12.5) [− 7.9 to 3.1]; *n* = 20
Improvement ≥ 5%, *n* (%)	5 (18.5); *n* = 27	4 (14.3); *n* = 28	9 (56.3); *n* = 16	6 (30.0); *n* = 20
KSQ General Health, % change from baseline, mean (SD) [95% CI]	9.43 (39.2) [− 5.4 to 24.2]; *n* = 27	2.30 (27.7) [− 10.9 to 15.5]; *n* = 17	1.46 (39.2) [− 17.7 to 20.7]; *n* = 16	4.22 (33.4) [− 9.8 to 18.2]; *n* = 22
Fatigue assessment scale, % change from baseline, mean (SD) [95% CI]	− 3.9 (20.7) [− 11.7 to 3.9]; *n* = 27	1.2 (24.0) [− 7.5 to 10.3]; *n* = 28	− 4.9 (28.1) [− 18.7 to 8.9]; *n* = 16	7.3 (36.2) [− 7.8 to 22.4]; *n* = 22

DLCO % predicted diffusing capacity of the lungs for carbon monoxide, *FVC* % predicted forced vital capacity, *KSQ* King's Sarcoidosis Questionnaire, *RCI* repository corticotrophin injection, *SD* standard deviation, *STS* sarcoidosis treatment score
[a]Baseline for all values is the last non-missing measurement prior to the first dose at the double-blind treatment phase

were found at week 48, with a two-fold higher mean STS in the RCI/RCI cohort (1.8) vs. the placebo/RCI cohort (0.9) (Table 2). The proportion of STS responders at week 24 was higher in the RCI group (59.3%) than in the placebo group (46.4%). Although the proportion of STS responders in subjects who received RCI throughout the entire study decreased to 40.9% at week 48, those who switched from placebo to RCI showed an increased responder rate of 52.0% (Fig. 4).

Pulmonary Function Tests

At week 24, the RCI group had a higher proportion of subjects with improvements ≥ 5% in FVC (37%) and DLCO (18.5%) compared with those in the placebo group (25% and 14.3%, respectively). At week 48, improvements ≥ 5%

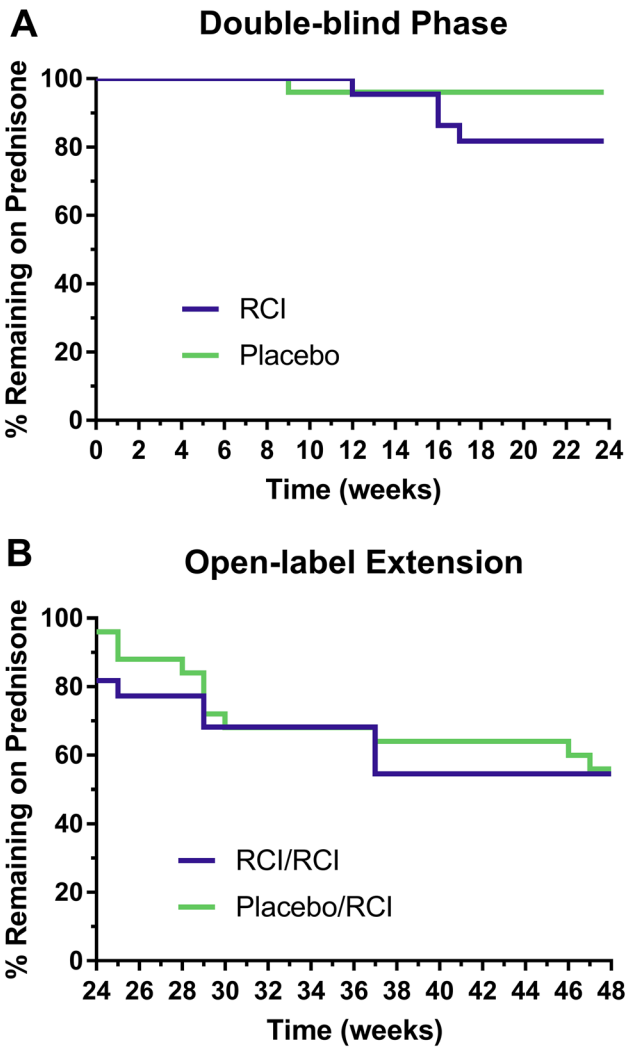


Fig. 3 Time to discontinuation of glucocorticoids without relapse through week 24 (**A**) and week 48 (**B**). Graphs represent subjects who completed both phases of the study. *RCI* indicates repository corticotropin injection

in the RCI/RCI group were observed in 12.5% and 56.3% of subjects for the absolute change in predicted FVC and DLCO, respectively, and in 30% of subjects in the placebo/RCI group for both FVC and DLCO (Table 2).

Lung Imaging

Likert scores (based on a five-point scale) for imaging analysis at week 24 indicated HRCT and chest X-ray improvement from baseline in two (7.4%) subjects in the RCI cohort, with no subjects worsening, whereas four (14.3%) subjects in the placebo group were deemed worse in both imaging assessments. Most subjects who received RCI (81.5% for HRCT and chest X-ray) or placebo (64.3% for HRCT and 67.9% for chest X-ray) were unchanged at week 24. At week 48, one subject in the RCI/RCI group exhibited improvement from baseline on both imaging assessments, whereas six (28.6%) and four (19%) subjects in the placebo/RCI cohort showed improvement in HRCT and chest X-ray, respectively. Similar to the DB phase, most of the imaging results for subjects in both cohorts at week 48 were unchanged (Fig. 5).

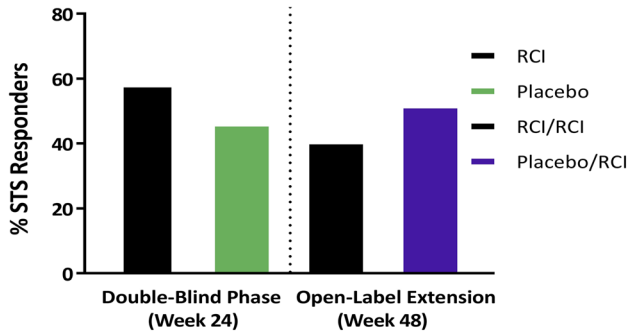


Fig. 4 STS responder rates at week 24 and week 48. *RCI* indicates repository corticotropin injection, *STS* sarcoidosis treatment score

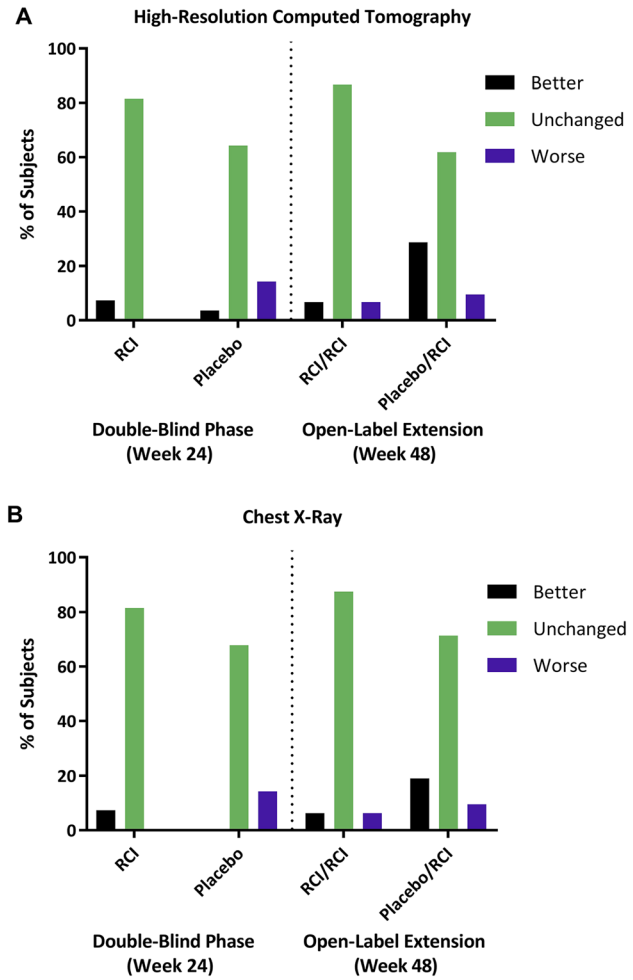


Fig. 5 Lung imaging assessments on HRCT (**A**) and X-ray (**B**) at week 24 and week 48. Some subjects did not have an evaluable result. "Better" indicates a $\geq$ 1 point improvement in Likert score, "worse" indicates $\geq$ 1 point score reduction, and "unchanged" indicates no change in score. *HRCT* indicates high-resolution computed tomography, *RCI* repository corticotropin injection

Patient-Reported Outcomes

Mean general health scores from the King's Sarcoidosis Questionnaire at week 24 showed an improvement from baseline of 9.43% in the RCI group vs. 2.3% in the placebo group. At week 48, the mean percentage change was 1.46% and 4.22% for RCI/RCI and placebo/RCI cohorts, respectively (Table 2). Improvements from baseline in Fatigue Assessment Scale scores (lower scores indicate less fatigue) were greater for RCI (− 3.9%) vs. placebo (1.2%) at week 24. At week 48, the mean changes were − 4.9% and 7.3% for the RCI/RCI and placebo/RCI groups (Table 2).

Safety

Twenty-five subjects (92.6%) in the RCI group and 27 (96.4%) in the placebo group reported at least one treatment-emergent adverse event (TEAE) during the DB phase. The most common TEAEs during the DB phase (occurring in ≥ 10% of all subjects) were fatigue (25% mild; 62.5% moderate; 12.5% severe), injection site bruising (100% mild), headache (58.3% mild; 33.3% moderate; 8.3% severe), cough (14.3% mild; 85.7% moderate), upper respiratory infection (71.4% mild; 28.6% moderate), arthralgia (71.4% mild; 28.6% moderate), and diabetes mellitus (20% mild; 80% moderate). In the OLE, 18 (81.8%) and 17 (68.0%) subjects in the RCI/RCI and placebo/RCI groups, respectively, reported one or more TEAEs, with cough being the most common TEAE across all subjects (occurring in 10.6%). The majority of TEAEs throughout the study were mild or moderate. Serious TEAEs occurred in four (14.8%) and six (27.3%) subjects in the RCI and RCI/RCI groups during DB and OLE phases, respectively, while serious TEAEs were experienced in three (10.7%) subjects in the placebo group and none of the subjects in the placebo/RCI group. TEAEs deemed related or possibly related to RCI were observed in 15 (55.6%), nine (40.9%), and five (20%) subjects in the RCI, RCI/RCI, and placebo/RCI groups, respectively, while 15 (53.6%) in the placebo group experienced treatment-related TEAEs (Table 3).

Post Hoc Subgroup Analysis

Subgroup analysis of STS responder rates for RCI and placebo at week 24 is presented in Supplemental Figure S1. The RCI cohort showed responder odds ratios (relative to the placebo cohort) that trended higher in several subgroup categories, including subjects with sarcoidosis duration ≤ 60 months, baseline DLCO ≤ 60%, baseline FVC ≤ 70%, and baseline sarcoidosis with multi-organ involvement (vs. only lung involvement), suggesting that these subgroups were more responsive to RCI compared to placebo.

DISCUSSION

The results of this study support that RCI was safe and well tolerated over long-term use and that the data trends suggest greater improvement with RCI vs. placebo in various efficacy endpoints. Subjects remaining on RCI through week 48 had a continued positive response, while those who switched from placebo to RCI showed similar improvements to those who received RCI throughout the entire study.

The results also suggest that addition of RCI to standard-of-care therapy may allow for a more rapid discontinuation of glucocorticoids in treatment of pulmonary sarcoidosis compared with placebo. After subjects receiving placebo were switched to RCI in the OLE, they showed a glucocorticoid discontinuation rate similar to the cohort who received RCI in the DB and OLE phases, such that both cohorts achieved comparable reductions of glucocorticoid use by week 48. This indicates that RCI had beneficial effects regardless of when it was started during the study. It is also important to note that approximately half of subjects receiving placebo had their glucocorticoid dosage tapered down during the first 24 weeks of the study, indicating that many patients with sarcoidosis are often maintained on higher prednisone doses than needed.

Other efficacy assessments suggested some improvement in pulmonary function, lung imaging, patient-reported outcomes, and STS for subjects receiving RCI vs. placebo at week 24

Table 3 Summary of TEAEs reported in ≥ 10% of ≥ 1 cohort and serious TEAEs

Adverse events, *n* (%)	Double-blind phase		Open-label extension	
	RCI (*n* = 27)	Placebo (*n* = 28)	RCI/RCI (*n* = 22)	Placebo/RCI (*n* = 25)
Any TEAE[a]	25 (92.6)	27 (96.4)	18 (81.8)	17 (68.0)
Fatigue	4 (14.8)	4 (14.3)[d]	2 (9.1)	2 (8.0)
Peripheral edema	3 (11.1)[b]	2 (7.1)[c]	1 (4.5)	1 (4.0)
Injection site bruising	2 (7.4)[c]	5 (17.9)[c]	1 (4.5)[f]	2 (8.0)[g]
Upper respiratory tract infection	5 (18.5)[b]	2 (7.1)	1 (4.5)[f]	0
Bronchitis	1 (3.7)[c]	2 (7.1)	3 (13.6)	0
Pneumonia	0	3 (10.7)[d]	1 (4.5)	0
Arthralgia	2 (7.4)	8 (28.6)	2 (9.1)	1 (4.0)
Back pain	0	3 (10.7)	1 (4.5)	1 (4.0)
Joint swelling	0	3 (10.7)	0	0
Cough	2 (7.4)	5 (17.9)[d]	3 (13.6)	2 (8.0)
Dyspnea	1 (3.7)	3 (10.7)	2 (9.1)	1 (4.0)
Dizziness	3 (11.1)[b]	1 (3.6)	1 (4.5)	0
Headache	4 (14.8)[b]	7 (25.0)[e]	1 (4.5)	0
Nausea	2 (7.4)[c]	2 (7.1)[d]	3 (13.6)[g]	1 (4.0)[f]
Gastrointestinal reflux	0	0	1 (4.5)	3 (12.0)
Diabetes mellitus	6 (22.2)	1 (3.6)	1 (4.5)[c]	1 (4.0)[c]
Contusion	3 (11.1)[b]	1 (3.6)	0	0
Sarcoidosis	3 (11.1)	1 (3.6)	0	1 (4.0)
Any serious TEAE[a]	4 (14.8)	3 (10.7)	6 (27.3)	0
Uveitis	1 (3.7)	0	0	0
Cholelithiasis	1 (3.7)	0	0	0
Influenza	1 (3.7)	0	0	0
Asthma	1 (3.7)	0	0	0
Diverticulitis	0	1 (3.6)	0	0
Pelvic abscess	0	1 (3.6)	0	0
Pneumonia	0	1 (3.6)[c]	1 (4.5)	0
Uterine leiomyoma	0	1 (3.6)	0	0
Gastrointestinal hemorrhage	0	0	1 (4.5)[f]	0

Table 3 continued

Adverse events, *n* (%)	Double-blind phase		Open-label extension	
	RCI (*n* = 27)	Placebo (*n* = 28)	RCI/RCI (*n* = 22)	Placebo/RCI (*n* = 25)
Decreased hemoglobin	0	0	1 (4.5)	0
Metastatic renal carcinoma	0	0	1 (4.5)	0
Pulmonary fibrosis	0	0	1 (4.5)	0
Pulmonary embolism	0	0	1 (4.5)[f]	0
Pulmonary hypertension	0	0	1 (4.5)	0
Respiratory failure	0	0	1 (4.5)	0

RCI repository corticotropin injection, *TEAE* treatment-emergent adverse event
[a]Subjects may have had more than one TEAE
[b]Two deemed related to study treatment
[c]All deemed related to study treatment
[d]One deemed related to study treatment
[e]Four deemed related to study treatment
[f]All deemed possibly related to study treatment
[g]One deemed possibly related study treatment

as well as in most efficacy endpoints after patients were switched from placebo to RCI in the OLE. Our results suggest that these assessments are reliable endpoints for use in future clinical trials.

Post hoc analysis revealed that several patient subgroups showed higher odds ratios for achievement of STS responder status following RCI treatment, suggesting that patients with specific baseline criteria, such as sarcoidosis diagnosed within the previous 5 years, may have a greater response to RCI. The subgroup analysis supports that RCI was effective for advanced disease with moderate to severe lung impairment and/or multi-organ disease. Despite faster weaning from steroids by those in the RCI group, there was a higher incidence of diabetes mellitus (n = 6, 22.2%) and more discontinuations (n = 1) due to this AE in the RCI group compared to the placebo group (n = 1, 3.6%; no discontinuations due to this AE) during the DB period. Only one subject in each group (placebo/RCI or RCI/RCI) during the OLE period exhibited diabetes mellitus. No major safety signals or AEs were identified in this study that would be unexpected during treatment of pulmonary sarcoidosis. The relatively low rate of serious TEAEs and infections suggests a favorable safety profile for RCI.

Our findings appear to be consistent with previously published clinical reports supporting the effectiveness of RCI in pulmonary sarcoidosis [7, 23, 24]. Given the unmet need for adequate treatment of refractory pulmonary sarcoidosis (i.e., disease that does not adequately respond to glucocorticoids), RCI may be an effective alternative or adjunctive therapy. Long-term and/or high-dose treatment with glucocorticoids is associated with increased risk of AEs such as infections, osteoporosis, cardiovascular disease, and psychiatric disorders [12]. Therefore, RCI may be preferrable due to its glucocorticoid-sparing effects [10, 12, 15]. Further, as the primary components of RCI are ACTH analogs, RCI likely functions via corticotropin-dependent activation of melanocortin receptors, which may induce both steroidogenic and non-steroidogenic mechanisms of action [18].

The primary limitation of this study was the relatively small sample size (N = 55). One hundred total subjects were planned to be

randomized, but the study was terminated early due to low enrollment, largely due to the COVID-19 pandemic. Therefore, the study was not sufficiently powered to determine statistically significant differences between treatment groups. We found that about half of the placebo-treated patients had their prednisone dose reduced during the 24 weeks of the DB phase, so future placebo-controlled trials of glucocorticoid sparing will need to include a large enough number of patients to account for this. A major strength of this study is the value provided from evaluation of long-term RCI treatment through 48 weeks, including detailed analyses of outcomes following glucocorticoid tapering [24]. To our knowledge, PULSAR was the third-largest DB, placebo-controlled, randomized clinical trial for sarcoidosis reported to date.

CONCLUSIONS

The results of this study provided insight on validation of endpoints, including a novel composite STS, which may be used in larger clinical trials for pulmonary sarcoidosis. This study demonstrated that RCI is a well-tolerated treatment for pulmonary sarcoidosis with trends in efficacy data that suggest greater improvement with RCI compared to placebo in patients receiving standard-of-care therapy. In addition, these findings support the need for larger trials to further confirm the efficacy of RCI in long-term management of pulmonary sarcoidosis.

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Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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