SAT0248

A Multicenter Study Assessing the Efficacy and Safety of Repository Corticotropin Injection in Patients With Rheumatoid Arthritis: Preliminary Interim Data From the Open-label Treatment Period

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Introduction

Rheumatoid Arthritis

- Rheumatoid arthritis (RA) is an autoimmune disorder associated with chronic inflammation, articular erosions, and periarticular bone loss[1]
  - Prevalence is estimated at 0.5% to 1.0% of adults in developed countries[1]
- The goal of treatment is the achievement of remission (absence of inflammatory disease); low disease activity (LDA) can be an acceptable alternative[2]
- Treatment options for patients with RA include disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids[2]
- An evaluation of reports of clinical studies revealed that 28%-58% of patients receiving DMARDs do not achieve a 20% improvement in American College of Rheumatology (ACR20) criteria,[3] highlighting the need for additional effective therapies for RA[2]

Repository Corticotropin Injection

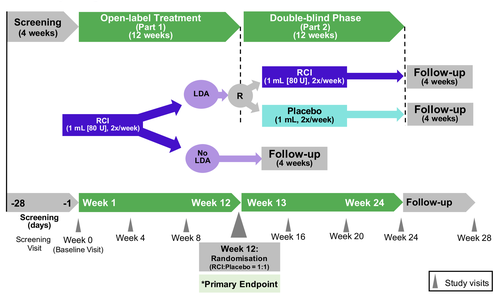
- Repository corticotropin injection (RCI; H.P. Acthar® Gel, Mallinckrodt ARD Inc., Hazelwood, MO) is approved in the United States as adjunctive therapy for short-term administration (during an acute episode or exacerbation) in RA (and selected cases may require low-dose maintenance therapy[4])
- RCI is a highly purified porcine adrenocorticotropic hormone (ACTH) analogue and an agonist for all 5 known melanocortin receptors (MCRs)[5]
  - Activation of MCRs by ACTH has been shown to have direct and indirect anti-inflammatory and immunomodulatory effects[6-8]
- In a small open-label single-centre study, 12 weeks of RCI was an effective add-on therapy for patients with active RA that was refractory to at least 3 therapeutic agents with different mechanisms of action[9]
- The current randomised, placebo-controlled study was conducted to confirm the efficacy and safety of RCI in patients with persistently active RA who continue to have suboptimal disease control in spite of standard of care

Study Objectives

- The efficacy and safety of RCI was evaluated in patients with persistently active RA despite receiving 1 to 2 DMARDs and corticosteroids
- This interim report summarises data collected through 19 April 2018

Methods

Figure 1. Study Design



*The proportion of patients who achieved LDA (DAS28-ESR <3.2) at Week 12.
Abbreviations: 2x/week, two times a week; DAS28-ESR, Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate; LDA, low disease activity; R, randomisation; RCI, repository corticotropin injection.

Study Design

- Ongoing multicentre, 2-part study (**Figure 1**)
- Patients with persistently active RA despite treatment with 1 to 2 conventional synthetic or biologic DMARDs (cs/bDMARDs) and corticosteroids were enrolled into the 12-week open-label treatment period (Part 1) and received RCI (1 mL; 80 U) subcutaneously (SC) twice a week for the entire 12-week period
- At Week 12, patients who achieved LDA entered the double-blind randomised phase (Part 2) and received
  - RCI (1 mL; 80 U) SC two times a week or
  - Placebo (1 mL) SC two times a week
- Patients who did not achieve LDA at Week 12 or who experienced an RA flare were discontinued from the study

Primary Endpoint

- The proportion of patients who achieved LDA at Week 12

Enrolment

- Target enrolment: 232 patients at up to 100 sites
- Patients who had signed informed consent and met all the eligibility criteria were enrolled (**Table 1**)
- Biologic and nonbiologic DMARDs that were allowed during the study are shown in **Table 2**

Table 1. Key Inclusion and Exclusion Criteria

Inclusion
Age ≥18 years
Meet the criteria for RA as defined by the 2010 ACR/EULAR classification
Have persistently active RA defined as a DAS28-ESR >3.2 despite treatment with required biologic/nonbiologic DMARD(s) and a corticosteroid
Currently taking a corticosteroid for 12 weeks and on a stable dose of prednisone (5-10 mg) for 4 weeks
Have been on at least 1 of the following for at least 12 weeks prior to the screening visit and must remain on same doses throughout the study: • Methotrexate ≤20 mg per week and 1 additional allowed biologic or nonbiologic DMARD (**Table 2**) • One allowed biologic DMARD (**Table 2**)
Exclusion
Have taken any investigational treatment for RA or biologic investigational agent ≤24 weeks or any nonbiologic investigational agent <6 weeks prior to the first dose of study drug
History of use of ACTH preparations for treatment of RA or sensitivity to ACTH
Currently has other rheumatic autoimmune disease or inflammatory joint disease
Used intraarticular corticosteroids <14 days prior to screening visit
Used B-cell–mediated therapies (ex, rituximab) <24 weeks prior to screening visit
Have known contraindications to RCI

Abbreviations: ACR, American College of Rheumatology; ACTH, adrenocorticotropic hormone; DAS28-ESR, Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate; DMARD, disease-modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; RCI, repository corticotropin injection.

Table 2. DMARDs Permitted During the Study

Nonbiologic DMARDs	Biologic DMARDs
Sulfasalazine	Infliximab
Leflunomide	Adalimumab
Hydroxychloroquine	Etanercept
Methotrexate	Certolizumab
	Golimumab
	Abatacept
	Tofacitinib*

*Targeted synthetic DMARD (tsDMARD).
Abbreviation: DMARD, disease-modifying anti-rheumatic drug.

Interim Study Assessments

- Efficacy was evaluated at baseline and Weeks 4, 8, and 12
  - Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate (DAS28-ESR) scores, including
    - Tender and swollen joint count
    - General Health Visual Analog Scale (VAS)
  - Proportion of patients who achieved LDA (defined as DAS28-ESR <3.2)
  - ACR response criteria with improvements of 20%, 50%, or 70%
  - Clinical Disease Activity Index (CDAI) responders (defined as CDAI score ≤10)
- Patient-reported outcomes (PROs) were assessed at baseline and Weeks 4, 8, and 12
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
  - Patient's assessment of physical function using the Health Assessment Questionnaire-Disability Index (HAQ-DI)
  - Work Productivity and Activity Impairment Questionnaire (WPAI)
  - Individual PRO components of the ACR criteria
    - Patient assessment of pain
    - Patient global assessment of disease activity
- Adverse events (AEs) were monitored and recorded throughout the study

Interim Results

Patient Disposition

- As of 19 April 2018, 58 patients had enroled, 48 patients had completed the 12-week open-label treatment period (Part 1), and 10 patients had discontinued
- The reasons for study discontinuation were
  - Withdrawal by the patients (n=6)
  - Lost to follow-up (n=1)
  - Met withdrawal criteria (n=1)
  - Other reasons (n=2)
- Demographics, baseline characteristics, and efficacy results are presented for the 48 patients who completed the 12-week open-label period; safety results are presented for the initial 58 patients who enroled in the study

Table 3. Demographics and Baseline Characteristics

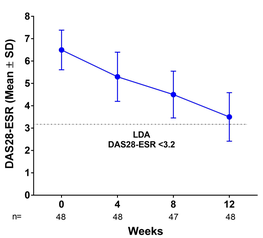
Characteristic	Patients who completed the open-label treatment period (N=48)
Age, y, mean (SD)	56.7 (11.55)
Female, n (%)	38 (79.2)
Race, n (%) American Indian or Alaska Native African American Caucasian	 5 (10.4) 5 (10.4) 38 (79.2)
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino	 28 (58.3) 20 (41.7)
Weight, kg, mean (SD)	73.2 (14.0)
DAS28-ESR score, mean (SD)	6.5 (0.9)
Tender Joint Count, mean (SD)	16.4 (7.0)
Swollen Joint Count, mean (SD)	12.2 (5.5)
CDAI, mean (SD)	41.2 (12.4)

Abbreviations: CDAI, Clinical Disease Activity Index; DAS28-ESR, Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate; SD, standard deviation.

Interim Efficacy Results

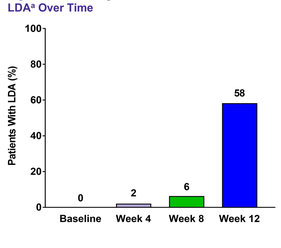
- RCI treatment decreased mean DAS28-ESR scores from baseline to Week 4 through Week 12 (**Figure 2**)
- The proportion of RCI-treated patients who achieved LDA increased over time during the open-label period (**Figure 3**)
- The percentage of patients treated with RCI who achieved an ACR20, ACR50, or ACR70 response increased over time from Week 4 through Week 12 of the open-label period (**Figure 4**)
- The proportion of patients who achieved CDAI LDA increased over time up to Week 12 (**Figure 5**)

Figure 2. Mean DAS28-ESR Scores Over Time



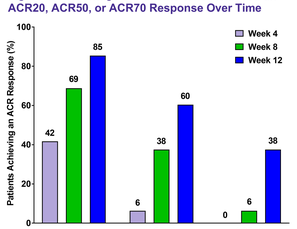
Mean DAS28-ESR values are reported as observed.
Abbreviations: DAS28-ESR, Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate; LDA, low disease activity; SD, standard deviation.

Figure 3. Percentage of Patients Who Achieved LDA[a] Over Time



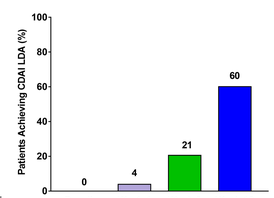
[a] LDA is defined as a DAS28-ESR score <3.2.
Abbreviations: DAS28-ESR, Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate; LDA, low disease activity.

Figure 4. Percentage of Patients Who Achieved an ACR20, ACR50, or ACR70 Response Over Time



Abbreviation: ACR, American College of Rheumatology.

Figure 5. Proportion of Patients Who Achieved CDAI LDA[a] Over Time



[a] CDAI LDA (defined as patients with CDAI score ≤10).
Abbreviations: CDAI, Clinical Disease Activity Index; LDA, low disease activity.

Interim PRO Results

- Overall, RCI treatment improved mean PRO scores from Week 4 through Week 12 (**Table 4**)

Table 4. Mean PRO Scores Over Time (n=48)

PRO Assessment	Baseline	Week 4	Week 8	Week 12	MCID
	Mean (SD)				
FACIT-F	25.8 (8.88)	19.5 (7.61)	18.6 (8.35)	15.7 (7.47)	3-4*[10]
HAQ-DI	1.7 (0.50)	1.3 (0.59)	1.0 (0.59)	0.8 (0.58)	0.22-0.25[10]
WPAI					
Percent work time missed due to RA	9.1 (12.92) n=*11*	16.9 (30.70) n=*13*	13.2 (18.52) n=*10*	8.7 (18.73) n=*10*	
Percent impairment while working due to RA	56.4 (28.38) n=*11*	45.0 (27.80) n=*12*	33.0 (24.06) n=*10*	29.0 (26.85) n=*10*	
Percent overall work impairment due to RA	59.5 (29.49) n=*11*	50.1 (30.03) n=*12*	40.6 (28.45) n=*10*	34.0 (30.81) n=*10*	
Percent activity impairment due to RA	69.6 (21.63)	54.8 (23.06)	40.8 (23.50)	33.3 (25.54)	
Patient assessment of pain	67.6 (20.50)	54.4 (21.29)	39.5 (20.76)	27.7 (22.46)	11[11]
Patient global assessment of disease activity	61.3 (21.23)	52.8 (17.67)	42.5 (21.76)	28.2 (23.37)	15% (absolute)/ 20% (relative improvement)#[12]

* Values represent the minimally important difference (MID) of 3-4 on a scale of 0-52.
# Values represent the minimum clinically important improvement (MCII).
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCID, minimum clinically important difference; PRO, patient-reported outcome; RA, rheumatoid arthritis; WPAI, Work Productivity and Activity Impairment Questionnaire.

Interim Safety Results

- To date, 28 patients (among the 58 enroled patients) reported at least 1 AE; the most common AEs in patients were headache (n=5; 8.6%) and hyperglycaemia (n=3; 5.2%)
- Two serious AEs (SAEs) were reported by 2 patients
  - One patient had chest pain radiating to the left arm, shortness of breath, dizziness, and weakness which the investigator deemed as unrelated to RCI; the SAE resolved, and the patient remained in the study
  - Another patient reported an SAE of pneumonia which the investigator assessed as "possibly related" to RCI; the patient withdrew from the study

Conclusions

- Interim data at 25% enrolment into the 12-week open-label arm of this ongoing trial support the efficacy of RCI in patients with persistently active RA despite treatment with corticosteroids and cs/bDMARD
  - RCI treatment decreased DAS28-ESR scores over time up to Week 12
  - Fifty eight percent of RCI-treated patients achieved LDA (DAS28-ESR <3.2) at Week 12
  - ACR 20/50/70 response was achieved by 85%, 60%, and 38% of patients at Week 12, respectively
  - Sixty percent of patients achieved CDAI LDA at Week 12
- Early data from patients treated with RCI suggest improvements in health outcomes as indicated by clinically meaningful numerical decreases in PRO scores from Weeks 4 to 12
- AEs observed were consistent with those in previous RCI trials, and no new safety signals were reported
- These interim results support the suggestion that RCI may be an effective and relatively safe treatment for patients with persistently active RA who were nonresponsive to corticosteroids and cs/bDMARD treatment

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Acknowledgement and Funding

Professional writing and editorial support was provided by MedLogix Communications, LLC, Itasca, Illinois, USA, under the direction of the authors and was funded by Mallinckrodt ARD Inc.