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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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Background

Rheumatoid Arthritis (RA)

- RA is an autoimmune disorder associated with chronic inflammation, articular erosions, and periarticular bone loss[1]
  - Prevalence is estimated at 0.5%-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]
- Disease-modifying anti-rheumatic drugs (DMARDs) are standard of care for patients with RA[2]
  - DMARD therapy is recommended immediately after RA diagnosis[2]
  - Corticosteroids are recommended as adjunct therapy during DMARD initiation or during a change in DMARDs[2]
- An evaluation 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 (RCI)

- 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
  - Selected cases may require low-dose maintenance therapy[4]
- RCI is a highly purified porcine adrenocorticotropic hormone (ACTH) analogue[5]
  - RCI and endogenous ACTH stimulate the adrenal cortex, and RCI binds to melanocortin receptors (MCRs)[4,5]
  - MCRs are present on tissue, immune, and organ cells throughout the body
  - Activation of MCRs by ACTH has been shown to have direct and indirect anti-inflammatory and immunomodulatory effects[6-8]
- In an open-label single-center 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 randomized, 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 despite standard of care

Study Objectives

- Evaluate the efficacy and safety of RCI in patients with persistently active RA despite receiving 1 or 2 DMARDs and corticosteroids
- Summarize data collected (50% of enrolled patients at Week 12) through May 10, 2018

Methods

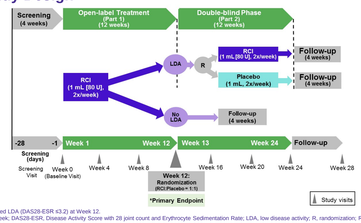
Study Design

- Ongoing, multicenter, 2-part study consisting of open-label (Part 1) and double-blind (Part 2) periods (**Figure 1**)
- Patients with persistently active RA despite treatment with 1 or 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 of the open label period, patients who achieved LDA, defined as achieving a Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate (DAS28-ESR) ≤3.2, entered the double-blind randomized period (Part 2)
- Patients who did not achieve LDA at Week 12 or who experienced an RA flare were discontinued from the study
  - *RA flare* is defined as an increase of >0.6 DAS28-ESR from Week 0 sustained over 2 consecutive visits or an increase of >1 DAS28-ESR from Week 0 at a single visit

Primary Endpoint

- The proportion of patients who achieved DAS28-ESR ≤3.2 (ie, LDA) at Week 12 of the open-label period

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, randomization; RCI, repository corticotropin injection.

Enrollment

- Target enrollment: 232 patients at up to 100 sites
  - Approximately 50% enrollment at Week 12 was assessed in this interim analysis
- 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 in the 12 weeks prior to the Screening Visit and on a stable dose of 5-10 mg of prednisone (or prednisone equivalent) for 4 weeks prior to the Screening Visit
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
Had 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 have other rheumatic autoimmune disease or inflammatory joint disease
Used intra-articular corticosteroids <14 days prior to screening visit
Used B-cell–mediated therapies (eg, 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	Golimumab
Leflunomide	Adalimumab	Abatacept
Hydroxychloroquine (HDQ)	Etanercept	Tofacitinib*
Methotrexate	Certolizumab	

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

Study Assessments

- Efficacy was evaluated at baseline and Weeks 4, 8, and 12
  - DAS28-ESR scores, including
    - Tender and swollen joint count
    - General Health Visual Analog Scale (VAS)
    - Erythrocyte Sedimentation Rate (ESR)
  - 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 patients with remission (>2.8)[10] and LDA (≤10)]
- Patient-reported outcomes (PROs) were assessed at baseline and Weeks 4, 8, and 12
  - Patient's assessment of physical function: Health Assessment Questionnaire-Disability Index (HAQ-DI)
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
  - Work Productivity and Activity Impairment Questionnaire (WPAI)
  - Individual PRO components of the ACR criteria
    - Patient assessment of pain and patient global assessment of disease activity
- Adverse events (AEs) were monitored and recorded throughout the study

Study Results

Patient Demographics

- As of May 10, 2018, 116 patients had enrolled, 100 had completed, 2 were ongoing, and 14 had discontinued the 12-week open-label period of the study

Table 3. Demographics and Baseline Characteristics

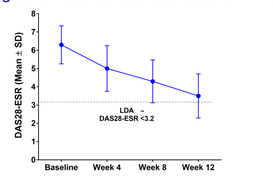
Characteristic	Patients Who Completed the Open-Label Treatment Period (n=100)
Age, y, mean (SD)	54.2 (11.53)
Female, n (%)	84 (84.0)
Race, n (%)	
American Indian or Alaska Native*	24 (24.0)
African American	7 (7.0)
Caucasian	61 (61.0)
Other or Not Reported	8 (8.0)
Weight, kg, mean (SD)	72.0 (14.51)
DAS28-ESR score, mean (SD)	6.3 (1.04)
Tender joint count (28 joint count), mean (SD)	14.8 (7.60)
Swollen joint count (28 joint count), mean (SD)	11.1 (5.31)
CDAI, mean (SD)	38.4 (12.93)

* Patient group includes South American Indians.
Data are mean (SD) where applicable.
Abbreviations: CDAI, Clinical Disease Activity Index; DAS28-ESR, Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate; SD, standard deviation.

Efficacy Results

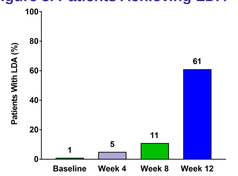
- RCI treatment, when utilized as adjunctive therapy to standard of care, decreased mean DAS28-ESR scores from baseline to Week 4 through Week 12 by a therapeutic gain of 2.8 (**Figure 2**)
- The proportion of RCI-treated patients who achieved LDA increased from Week 8 to Week 12 during the open-label period (**Figure 3**)

Figure 2. Mean DAS28-ESR Scores



Mean DAS28-ESR values are reported as observed. LDA is defined as a DAS28-ESR score ≤3.2; n=100 at each time point.
Abbreviations: DAS28-ESR, Disease Activity Score with 28 joint count and erythrocyte sedimentation rate; LDA, low disease activity; SD, standard deviation.

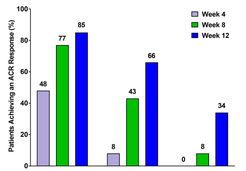
Figure 3. Patients Achieving LDA[a]



[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.

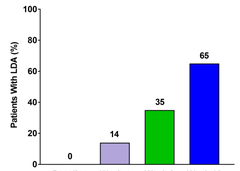
- The percentage of patients treated with RCI who achieved ACR20, ACR50, or ACR70 responses through Week 12 of the open-label period are shown in **Figure 4**
- The proportion of patients who achieved significant clinical improvement of their RA symptoms, as indicated by CDAI LDA, in the open-label period are shown in **Figure 5**

Figure 4. Patients Achieving ACR20, ACR50, or ACR70 Response



Abbreviation: ACR, American College of Rheumatology.

Figure 5. Proportion of Patients Achieving CDAI LDA[a]



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

PRO Results

Table 4. Mean PRO Scores in the Open-Label Period (n=100)

PRO Assessment	Baseline	Week 4	Week 8	Week 12	MCID
	Mean (SD)				
FACIT-F	22.6 (8.69)	17.2 (8.08)	16.1 (8.24)	13.8 (7.36)	3-4[a11]
HAQ-DI	1.6 (0.54)	1.1 (0.64)	0.9 (0.66)	0.7 (0.60)	0.22[a11]
Patient global assessment of disease activity	60.8 (19.58)	45.9 (19.93)	35.3 (21.66)	24.4 (20.47)	15% (absolute)/ 20% (relative improvement)[a12]
WPAI					
Percent work time missed due to RA	17.1 (22.77)	17.6 (25.55)	13.1 (16.88)	8.8 (13.76)	ND
Percent impairment while working due to RA	46.2 (26.39)	30.7 (25.95)	25.6 (18.88)	20.4 (20.09)	ND
Percent overall work impairment due to RA	52.8 (27.55)	39.4 (30.68)	34.6 (23.71)	26.6 (23.62)	ND
Percent activity impairment due to RA	62.0 (22.96)	45.9 (26.75)	36.1 (22.69)	28.2 (23.88)	ND
Patient assessment of pain	64.8 (19.55)	47.0 (22.94)	34.8 (21.00)	24.4 (21.55)	11[a13]

[a] Values represent the minimally important difference (MID) of 3-4 on a scale of 0-52.
[a] 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; ND, MCID not determined; PRO, patient-reported outcome; RA, rheumatoid arthritis; WPAI, Work Productivity and Activity Impairment Questionnaire.

Table 5. Adverse Events[a] and Study Withdrawals

Event	Patients (N=116) n (%)
Infections and infestations	17 (14.7)
Urinary tract infection	4 (3.4)
Pharyngitis	3 (2.6)
Nasopharyngitis	2 (1.7)
Otitis media acute	2 (1.7)
Upper respiratory tract infection	2 (1.7)
General disorders and administration site conditions	10 (8.6)
Pain	2 (1.7)
Nervous system disorders	10 (8.6)
Headache	10 (8.6)
Injury, poisoning, and procedural complications	6 (5.2)
Contusion	2 (1.7)
Fall	2 (1.7)
Joint dislocation	2 (1.7)
Musculoskeletal and connective tissue disorders	6 (5.2)
Skin and subcutaneous tissue disorders	5 (4.3)
Investigations (ie, blood glucose increased, blood pressure increased, systolic blood pressure increased, liver function test increased)	4 (3.4)
Metabolism and nutrition disorders	4 (3.4)
Hyperglycemia	3 (2.6)
Gastrointestinal disorders	3 (2.6)
Psychiatric disorders	3 (2.6)
Cardiac disorders	2 (1.7)
Ear and labyrinth disorders	2 (1.7)
Renal and urinary disorders	2 (1.7)
Serious adverse events	2 (1.7)
Chest pain	1 (0.9)
Pneumonia	1 (0.9)
Study withdrawals	14 (12.1)
Withdrawal by subject	9 (7.8)
Adverse event	0 (0.0)
Met withdrawal criteria	1 (0.9)
Death	0 (0.0)
Other	4 (3.4)

[a] List of adverse events with ≥2 occurrences. Subjects with multiple occurrences for an event are counted only once.

Limitations

- These are results of 50% of patients enrolled at Week 12; results may change when the study is fully enrolled
  - Because this is an interim report, significance tests were not conducted; thus, *P*-values are not reported
- These results are from an open-label period; patients could not advance to the double-blind portion without achieving LDA by Week 12. Because this was known by the patients and investigators, there may have been a subconscious motivation in a majority of patients to dramatically "improve" between Weeks 8 and 12 rather than RCI becoming effective from Weeks 8 to 12
- Since patients continued use of cs/bDMARDs and corticosteroids, study effects may not be completely attributed to RCI

Conclusions

- The data at approximately 50% enrollment into the 12-week open-label arm of this ongoing trial appear to support the efficacy of RCI in patients with persistently active RA despite treatment with corticosteroids and cs/bDMARDs
  - DAS28-ESR scores improved with RCI treatment by Week 12
  - DAS28-ESR LDA was achieved in 61% of patients with RCI at Week 12
  - ACR 20/50/70 response was achieved by 85%, 66%, and 34% of patients at Week 12, respectively
  - CDAI LDA was achieved by 65% of patients at Week 12
- There were clinically meaningful improvements in HAQ-DI, FACIT-F, and patient assessment of pain with RCI during the open-label period
- AEs observed were consistent with those in previous RCI trials, and no new safety signals were reported
- These interim results suggest that RCI may be an effective and safe treatment for patients with persistently active RA who had a suboptimal response to corticosteroids and cs/bDMARD treatment
  - Similar results would have to be shown in a prospective double-blind study to confirm these observations

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