A Multicentre Study Assessing the Efficacy and Safety of Repository Corticotropin Injection in Patients With Persistently Active Rheumatoid Arthritis

Roy Fleischmann,[1] Daniel E. Furst,[2] Erin Connolly-Strong,[3] Jingyu Liu,[3] Julie Zhu,[3] and Richard Brasington[4]

[1]University of Texas Southwestern Medical Center – Dallas, TX, USA; [2]David Geffen School of Medicine at UCLA – Los Angeles, CA, USA; [3]Mallinckrodt ARD, LLC – Bedminster, NJ, USA; [4]Washington University School of Medicine – St. Louis, MO, USA

Introduction

Rheumatoid Arthritis (RA) Treatment

- Despite the availability of several disease-modifying antirheumatic drugs (DMARDs), many patients with RA have persistent disease activity and do not achieve an adequate response
- Both the European League Against Rheumatism[1] and the American College of Rheumatology (ACR)[2] recommend only short-term administration of corticosteroids in patients with RA, for their anti-inflammatory effects

Repository Corticotropin Injection (RCI)

- A naturally sourced complex mixture of purified adrenocorticotropic hormone analogues and other pituitary peptides
- An agonist for all 5 melanocortin receptors
- Approved in the United States for short-term administration in RA
- Shown in open-label studies to benefit patients with RA who have not responded adequately to other therapies[3,4]

Objective and Scope

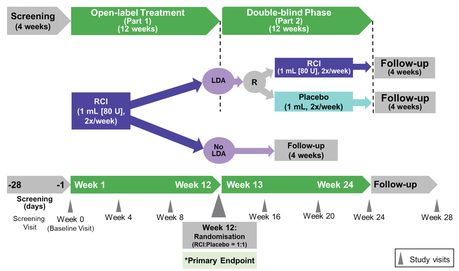
- This study assesses the efficacy and safety of RCI in subjects with persistently active RA despite the use of a corticosteroid and 1 or 2 DMARDs
- Results from the open-label and double-blind, placebo-controlled, randomised withdrawal periods are presented here

Methods

Design and Participants

- Multicentre 2-part study (**Figure 1**)
  - Part 1: 12-week open-label RCI treatment period
  - Part 2: 12-week, double-blind, placebo-controlled, randomised withdrawal period for subjects who achieved low disease activity (LDA), defined as disease activity score with 28 joint count and erythrocyte sedimentation rate (DAS28-ESR) <3.2, during Part 1

Figure 1. Study Design



Abbreviations: LDA, low disease activity; R, randomisation; RCI, repository corticotropin injection.

Table 1. Key Inclusion and Exclusion Criteria

Inclusion	Exclusion

• Age ≥18 years
• Meet criteria for RA as defined by the 2010 ACR/EULAR classification[5] at screening
• Persistently active RA, defined as DAS28-ESR >3.2 despite treatment with required biologic/nonbiologic DMARD(s) and a CS at screening and baseline
• Use of a CS in the 12 weeks before screening and on a stable dose of 5-10 mg of prednisone (or equivalent) for 4 weeks before screening
• Use of 1 of the following for ≥12 weeks before screening (and must remain on same doses throughout study)
  • Methotrexate ≤20 mg/wk and 1 biologic/nonbiologic DMARD (see Table 2)
  • One allowed biologic DMARD
	• Use of any investigational treatment for RA or any biologic investigational agent during the 24 weeks before the first dose of study drug or any nonbiologic investigational agent within 6 weeks before the first dose of study drug
	• History of sensitivity to ACTH preparations or use of ACTH preparations for RA
	• Current rheumatic autoimmune disease or inflammatory joint disease other than RA
	• Use of intra-articular CSs in the 14 days before screening
	• Use of B-cell–mediated therapies (eg, rituximab) in the 24 weeks before screening
	• Known contraindications to RCI

Abbreviations: ACR, American College of Rheumatology; ACTH, adrenocorticotropic hormone; CS, corticosteroid; DAS28-ESR, disease activity score with a 28 joint count and erythrocyte sedimentation rate; DMARD; disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; RCI, repository corticotropin injection.

Table 2. Permitted DMARDs

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

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

Primary Efficacy Endpoint

- Proportion of subjects with LDA (DAS28-ESR <3.2) at Week 12

Secondary and Exploratory Endpoints

- Disease activity flare rate at Week 24
  - *Disease activity flare* was defined as fulfillment of any of the following criteria:
    - DAS28-ESR <3.2 and an increase of 1.2 from Week 12
    - DAS28-ESR ≥3.2 and an increase of >0.6 from Week 12, sustained for 2 consecutive study visits
    - DAS28-ESR ≥3.2 and an increase of >1 from Week 12 at a single visit
- Proportion of subjects who maintained LDA (DAS28-ESR <3.2) from Weeks 12 to 24
- Proportion of subjects with Clinical Disease Activity Index (CDAI) score ≤10 at Week 12, and who maintained CDAI score ≤10 from Weeks 12 to 24
- Proportion of subjects who met the ACR20, ACR50, and ACR70 criteria[5]

Safety Endpoints

- Serious and nonserious adverse events (AEs)

Exploratory Pharmacodynamic Endpoints

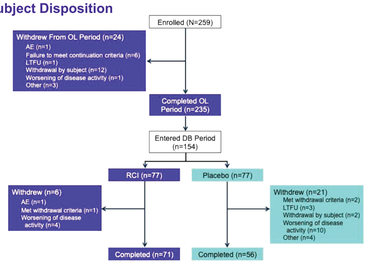
- Serum and urine bone turnover markers

Results

Efficacy

- Efficacy results are presented for the modified intent-to-treat (mITT) population, which includes all subjects who received ≥1 dose of study drug and contributed any efficacy data to the study

Figure 2. Subject Disposition



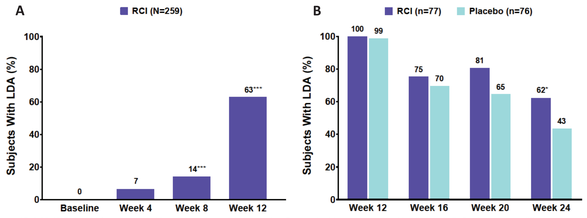
Abbreviations: AE, adverse event; DB, double-blind; LTFU, lost to follow-up; OL, open-label; RCI, repository corticotropin injection.

Table 3. Subject Demographics and Baseline Characteristics (Safety Population)

Characteristic	Open-label	Double-blind	
	RCI (N=259)	RCI (n=77)	Placebo (n=76)
Age, mean (SD), y	51.0 (12.2)	50.1 (12.2)	50.9 (11.3)
Female sex, no. (%)	231 (89)	67 (87)	69 (90)
Race, no. (%)			
White	170 (66)	53 (69)	53 (69)
African American	15 (6)	1 (1)	2 (3)
Asian	3 (1)	0	1 (1)
American[a] Indian or Alaska Native	40 (15.4)	12 (16)	14 (18)
Other or not reported	31 (12)	11 (14)	7 (9)
Weight, mean (SD), kg	72.9 (17.0)	70.8 (15.7)	72.4 (14.5)
DAS28-ESR, mean (SD)	6.3 (1.0)	6.2 (0.9)	6.2 (1.0)
ESR, mean (SD)	43.6 (24.8)	40.3 (21.5)	42.0 (22.9)
DAS28-ESR at Week 12, mean (SD)	3.6 (1.4)	2.8 (0.4)	2.7 (0.5)
ESR at Week 12, mean (SD)	24.0 (21.5)	15.8 (12.2)	15.2 (12.6)

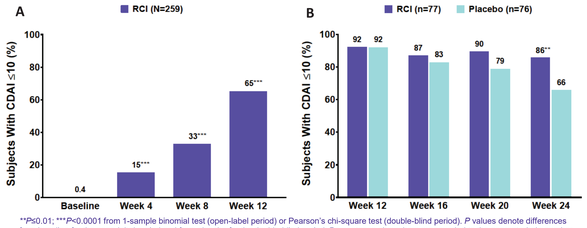
[a]North, Central, or South American Indian. **Abbreviations**: DAS28-ESR, disease activity score with 28 joint count and erythrocyte sedimentation rate; RCI, repository corticotropin injection; SD, standard deviation.

Figure 3. Proportions of Subjects Achieving LDA Defined by DAS28-ESR <3.2 During the Open-label Period (A) and Proportions of Subjects Maintaining LDA During the Double-blind, Placebo-Controlled, Randomised Withdrawal Period (B), mITT Population



*P≤0.05; ***P<0.0001 from 1-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. **Abbreviations**: DAS28-ESR, disease activity score with 28 joint count and erythrocyte sedimentation rate; LDA, low disease activity; mITT, modified intent-to-treat; RCI, repository corticotropin injection.

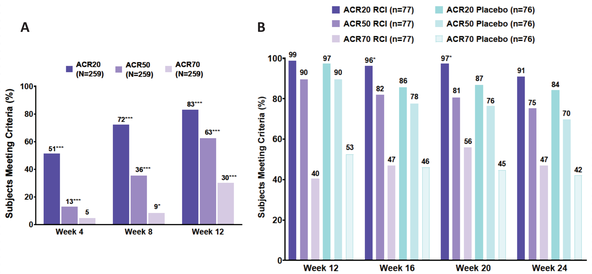
Figure 4. Proportions of Subjects Achieving CDAI ≤10 During the Open-label Period (A) and Proportions of Subjects Maintaining CDAI ≤10 During the Double-blind, Placebo-Controlled, Randomised Withdrawal Period (B), mITT Population



P≤0.01; ***P<0.0001 from 1-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. **Abbreviations: CDAI, Clinical Disease Activity Index; mITT, modified intent-to-treat; RCI, repository corticotropin injection.

- 63% of subjects achieved LDA after 12 weeks of treatment with open-label RCI
- At Week 24, the cumulative disease activity flare rate was significantly lower for the RCI group (17.05%) than for the placebo group (29.73%; *P*=0.049) [data not shown]
- At Week 24, a significantly greater proportion of RCI-treated subjects than placebo-treated subjects achieved LDA

Figure 5. Proportions of Subjects Who Met ACR Criteria During the Open-label (A) and Double-blind, Placebo-Controlled, Randomised Withdrawal (B) Periods, mITT Population



*P≤0.05; ***P<0.0001 from 1-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. **Abbreviations**: ACR, American College of Rheumatology; mITT, modified intent-to-treat; RCI, repository corticotropin injection.

Table 4. Changes in Other Efficacy Outcome Measures During the Open-label Period, mITT Population

Outcome	Change From Baseline, Mean (SD)			MID/MCID
	Week 4	Week 8	Week 12	
DAS28-ESR	−1.4 (1.1)**	−2.0 (1.2)**	−2.8 (1.4)**	1.2[6]
Swollen joint count	−5.3 (5.0)**	−6.9 (5.0)**	−8.1 (5.4)**	ND
Tender joint count	−7.0 (6.6)**	−8.9 (7.0)**	−10.7 (7.8)**	ND
FACIT-F	−5.0 (8.2)**	−6.5 (8.4)**	−8.7 (8.4)**	3-4[7]
HAQ-DI	−0.5 (0.5)**	−0.6 (0.6)**	−0.8 (0.6)**	0.22-0.25[7]

P<0.001 from 1-sample *t* test. **Abbreviations: DAS28-ESR, disease activity score with 28 joint count and erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCID, minimally important clinical difference; MID, minimally important difference; mITT, modified intent-to-treat; ND, not determined; SD, standard deviation.

Table 5. AEs of Interest (Safety)

Adverse Event	No. (%) of Subjects		
	Open-label	Double-blind	
	RCI (N=259)	RCI (n=77)	Placebo (n=77)
Any AE	98 (38)	25 (33)	31 (40)
Diabetes mellitus	1 (0.4)	1 (1)	0
Glycosylated haemoglobin increased	4 (2)	1 (1)	2 (3)
Liver function test increased	1 (0.4)	0	1 (1)
Hyperglycaemia	3 (1)	3 (4)	2 (3)
Hypertension	4 (2)	3 (4)	0
Weight increased	0	0	1 (1)

Abbreviations: AE, adverse event; RCI, repository corticotropin injection; SD, standard deviation.

Table 6. Bone Turnover Markers, mITT Population (Safety)

Marker	Mean (SD)		*P* value
	Baseline	Week 12	
CTX, ug/L	4.8 (2.1)	4.8 (1.9)	0.866
CTX-I, ug/L	0.4 (0.2)	0.4 (0.2)	0.956
CTX-II, ug/L	3.5 (2.3)	3.0 (2.2)	0.006
CTX-II CRT, ng/mmol	452.4 (325.4)	362.5 (273.1)	<0.001
OPG, pmol/L	4.7 (1.8)	4.7 (2.0)	0.997
P1NP, ug/L	52.2 (28.2)	47.4 (26.2)	0.004
sRANKL, pmol/L	2057.7 (3592.9)	2107.6 (3794.6)	0.284

Abbreviations: CRT, creatinine; CTX, C-terminal cross-linking telopeptide; CTX-I, C-terminal cross-linking telopeptide of type I collagen; CTX-II, C-terminal cross-linking telopeptide of type II collagen; mITT, modified intent-to-treat; OPG, osteoprotegerin; P1NP, N-terminal propeptide of type I collagen; SD, standard deviation; sRANKL, soluble receptor activator of nuclear factor kappa-β ligand.

Summary

Open-label Period

- During the open-label period, RCI therapy was associated with significant improvements in
  - Disease activity scores (DAS28-ESR and CDAI)
  - Swollen and tender joint counts
  - Measures of fatigue (FACIT-F) and physical function (HAQ-DI)
  - The proportions of subjects who met the ACR 20/50/70 criteria had significantly increased **(Figure 5A)**
- Markers of bone turnover were mostly stable, indicating no effect of RCI on bone metabolism

Double-blind, Placebo-Controlled, Randomised Withdrawal Period

- For those patients who achieved LDA defined by DAS28-ESR <3.2 at Week 12, and entered the double-blind, placebo-controlled, randomised withdrawal period, at Week 24
  - Significantly more subjects in the RCI group than in the placebo group had maintained LDA, as assessed by the DAS28-ESR
  - Significantly more subjects in the RCI group than in the placebo group had maintained CDAI ≤10, as another evidence of low disease activity
  - There was a sustained effect of RCI on DAS28-ESR <3.2 **(Figure 3B)**, CDAI ≤10 **(Figure 4B)**, and ACR 20/50/70 **(Figure 5B)**
  - Cumulative disease activity flare rate was significantly lower in the RCI group than in the placebo group
- By Week 24 of the double-blind, placebo-controlled, randomised withdrawal phase, there was a sustained effect of RCI on the disease activity **(Figure 5B)**

Safety

- No new safety signals were noted

Conclusion

- In this study, RCI appeared to be safe and effective, and showed sustained effect in patients who have persistently active RA despite corticosteroid/DMARD therapy

References

1. Smolen JS, et al. *Ann Rheum Dis*. 2017;76(6):960-977. **2.** Singh JA, et al. *Arthritis Rheumatol*. 2016;68(1):1-26. **3.** Gillis T, et al. *Open Access Rheumatol*. 2017;9:131-138. **4.** Fischer PA and Rapoport RJ. *Open Access Rheumatol*. 2018;10:13-19. 5. Aletaha D, et al. *Arthritis Rheum*. 2010;62(9):2569-2581. 6. Curtis JR, et al. *Arthritis Care Res (Hoboken)*. 2015;67(10):1345-1353. **7.** Orbai AM and Bingham CO, 3rd. *Curr Rheumatol Rep*. 2015;17(4):28.

Acknowledgement and Funding

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

Presented at the European League Against Rheumatism (EULAR) Congress • Madrid, Spain • 12-15 June 2019