Study Design of the Randomized, Double-blind, Placebo-Controlled OPTIONS Study of Repository Corticotropin Injection for Acute Exacerbations of RRMS

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Introduction

- Despite availability of effective disease-modifying therapies (DMTs), some patients with relapsing-remitting multiple sclerosis (RRMS) continue to experience acute exacerbations
- Relapses in RRMS patients are associated with impaired capabilities, residual disability, and reduced quality of life (QoL)[1,2]
- High-dose steroids are the standard of care for relapses, but patients who have residual deficits following treatment with high-dose corticosteroids have limited treatment options
- Repository corticotropin injection (RCI; Acthar® Gel) is approved by the US Food and Drug Administration for the treatment of RRMS exacerbations.[3] RCI is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides[3]
- The therapeutic benefits of RCI are often ascribed to corticosteroid production; however, recent evidence suggests that the immunomodulatory and anti-inflammatory effects of RCI may be mediated via corticosteroid-independent melanocortin receptor signaling pathways[4]
- The objective of this ongoing multicenter, randomized, double-blind, placebo-controlled, parallel-group OPTIONS trial is to assess the response rate, safety, and tolerability of RCI in patients with RRMS who have not responded to high-dose corticosteroids
- Interim baseline characteristics (50% of enrollment) are provided

Methods

Patients and study design

- Subjects with RRMS who have experienced a relapse and who will receive, within 28 days of symptom onset, 3 to 5 days (given over a period of up to 7 days) of treatment with:
  - High-dose intravenous methylprednisolone (1,000 mg/d)
  - oral prednisone (1,250 mg/d), or
  - oral methylprednisolone (1,000 mg/d)
- A study design schematic is presented in **Figure 1,** and a list of assessments is presented in **Table 1**. Key inclusion and exclusion criteria are presented in **Table 2**
- Screening visits will take place during the initial 28 days of the 42-day screening period during which subjects will be assessed with the Expanded Disability Status Scale (EDSS)/Functional Systems Score (FSS) prior to treatment with corticosteroids
- At 14 (±1) days following the initiation of high dose corticosteroids, subjects will be reassessed with the EDSS/FSS
  - Subjects who do not improve by at least 1 point in one or more functions of the FSS will be randomized on a 1:1 basis to receive subcutaneous (SC) RCI 1 mL (80 U/d or SC matching placebo 1 mL/d for 14 days

Primary objectives

- Generate an estimate of the response rate for RCI
- Assess the safety and tolerability of RCI

Secondary objective

- Assess the effect of RCI on QoL

Exploratory objective

- Explore the effect of RCI on work productivity and health outcome measures

Efficacy and safety assessments

- Efficacy evaluations:
  - Multiple Sclerosis Impact Scale Version 1 (MSIS-29v1)
  - EDSS/FSS
  - Clinical Global Impression of Improvement (CGI-I) Scale

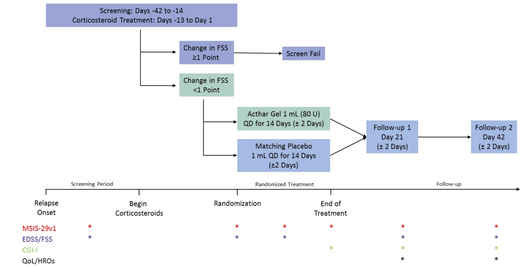
Methods (cont'd)

- Safety evaluations:
  - Adverse events, physical examinations, clinical laboratory tests, pregnancy testing, medical history, weight, and vital signs
- QoL/health outcomes evaluations:
  - Health Resource Utilization (HRU), Centers for Disease Control and Prevention Healthy Day Core Module (CDC-HRQoL-4), and Work Productivity and Activity Impairment Instrument (WPAI)
- Responses will be evaluated up to 42 days after randomization using the EDSS/FSS, MSIS-29v1, and CGI-I scales

Statistical analyses

- Primary efficacy endpoint
  - EDSS response rate and 90% confidence interval at Day 42, defined as the percentage of patients with an EDSS score improvement (decrease) of ≥1.0 point (if ≤5.5 at baseline) or ≥0.5 point (if >5.5 at baseline)
- Primary safety endpoint
  - A summary of general safety profile, including adverse events (serious and nonserious), vital signs, and laboratory assessments by study period and over the entire study
- Because of the small size of this study, no inferential statistics are planned

Figure 1. Study Design Schematic



Abbreviations: FSS, Functional Systems Score; CGI-I, Clinical Global Impression of Improvement; EDSS/FSS, Expanded Disability Status Scale/Functional Systems Score; HRO, health-related outcome; MSIS-29v1, Multiple Sclerosis Impact Scale Version 1; QD, once per day; QoL, quality of life.

Table 1. Timing of Study Assessments

	MSIS-29v1	EDSS/FSS	CGI-I	QoL/HROs[1]
Screening (Days −42 to −14)	X[2]	X[2]		
Randomization (Baseline)	X	X		X
Treatment Day 7 (±1 Day)	X	X	X	
End of Treatment (Day 14 ±2 Days)	X			
Follow-up 1 (Day 21 ±2 Days)	X	X	X	X
Follow-up 2 (Day 21 ±2 Days)	X	X	X	X

[1]QoL/HRO assessments: Centers for Disease Control and Prevention Healthy Days Core Module, Health Resource Utilization Questionnaire, and Work Productivity and Activity Impairment Questionnaire.
[2]Screening assessment may be obtained up to 2 days after initiation of high-dose corticosteroids.
Abbreviations: CGI-I, Clinical Global Impression of Improvement; EDSS/FSS, Expanded Disability Index Scale/Functional Systems Score; HRO, health-related outcome; MSIS-29v1, Multiple Sclerosis Impact Scale Version 1; QoL, quality of life.

Table 2. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Subjects must be ≥18 years of age at the Screening Visit and can be male or female • Must have a diagnosis of RRMS according to the revised McDonald criteria[5] • Must have had a relapse with onset ≤42 days prior to the Baseline Visit • Must have started 3 to 5 days (given over a period of up to 7 days) of corticosteroid treatment within 28 days of the onset of the first relapse symptom • Must have failed to obtain an improvement of at least 1 point in 1 or more functions on the FSS 14 days following the first dose of high-dose corticosteroids • Must have an EDSS score of 2.0 to 6.5 at the Baseline Visit • Must have a mean systolic blood pressure ≤140 mm Hg and a mean diastolic blood pressure of ≤90 mm Hg at the Screening and Baseline Visits	• Subject has used RCI for the treatment of MS within the last 6 months • Has only sensory, bowel/bladder, and/or cognitive symptoms of MS associated with the most recent relapse • Has been treated with daclizumab or any immunosuppressants in the 6 months prior to the Screening Visit or throughout the study. Subjects treated with natalizumab will be excluded if they are not currently negative for John Cunningham virus • Subjects receiving any non-excluded disease-modifying treatments must have been on a stable dose(s) for 30 days prior to the Baseline Visit and plan to remain on that dose(s) throughout the study • Has type 1 or type 2 diabetes mellitus • Has certain specified laboratory test abnormalities at the Screening Visit

Abbreviations: EDSS, Expanded Disability Index Scale; FSS, Functional Systems Score; RCI, repository corticotropin injection; RRMS, relapsing-remitting multiple sclerosis.

Results

Results (50% of enrollment target)

- Baseline data (**Table 3**) are from 32 patients (approximately 50% of the 66-patient target). Mean age is 42.2 years (78.1% female, 84.4% Caucasian)
- Average time since MS diagnosis is 13.7 years, and mean EDSS score at baseline is 3.91. DMTs used at baseline are glatiramer acetate (9), teriflunomide (6), alemtuzumab (3), dimethyl fumarate (2), fingolimod (2), or interferon beta-1b (1)

Table 3. Baseline Characteristics

Characteristic	Total (N=32)
Age (Years), Mean (SD)	42.2 (11.6)
Sex, n (%)	
Female	25 (78.1)
Male	7 (21.9)
Race, n (%)	
Black or African American	5 (15.6)
White	27 (84.4)
Time Since MS Diagnosis, Mean (SD)*	13.7 (9.7)
EDSS Score at Baseline, Mean (SD)	3.9 (1.2)
DMT at Baseline, n (%)	
Glatiramer Acetate	9 (39.1)
Teriflunomide	6 (26.1)
Alemtuzumab	3 (13.0)
Dimethyl Fumarate	2 (8.7)
Fingolimod	2 (8.7)
Interferon Beta-1b	1 (4.4)

*N=24
Abbreviations: DMT, disease-modifying treatment; EDSS, Expanded Disability Index Scale; MS, multiple sclerosis; SD, standard deviation.

Conclusions

- Baseline characteristics indicate that the enrolled subjects are broadly representative of the RRMS population
- It is hoped that this pilot study will provide some guidance for the planning of a larger study of the treatment of RRMS with RCI
- Results of the OPTIONS trial are intended to support RCI as an effective treatment for acute exacerbations of RRMS in patients with inadequate response to high-dose steroids

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